



ADVANCES IN HETEROCYCLIC CHEMISTRY

Volume 19

A. R. Katritzky &
A. J. Boulton

Advances in
Heterocyclic
Chemistry

Volume 19

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Advances in
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CHEMISTRY

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Preface

The present volume consists of four chapters. The first (by Ollis and Ramsden) classifies and discusses the chemistry of that interesting group of compounds known as meso-ionic heterocycles and includes a useful general definition of the term. The second chapter (Litvinov and Gol'dfarb) deals with systems with two (or more) thiophene (or selenophene) rings directly fused together. The 1,2,3-triazines, along with the better-known 1,2,3-benzotriazines and other fused 1,2,3-triazine systems, are discussed in the third chapter, by Kobylecki and McKillop. In the last chapter George, Khetan, and Gupta treat heterocyclic syntheses which involve the addition of nucleophilic reagents to acetylenic esters.

A. R. KATRITZKY
A. J. BOULTON

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Correction

“Cationic Polar Cycloaddition” by Charles K. Bradsher, Volume 16,
page 303

In this review, the suggestion was made that the structure of the diadducts obtained by Fuks, King, and Viehe through reaction of the 2-methylisoquinolinium ion should be reexamined to make certain that the initial addition was really $2 + 2$ as proposed and not $4 + 2$. This suggestion was based upon a feeling that alkenes and ynamines should behave similarly in cycloaddition and was encouraged by the moderately large discrepancy factor (.22) reported by Fuks *et al.* for their single crystal X-ray diffraction.

Thanks to the collaboration of Professor M. Van Meerssche and at the request of Professor H. G. Viehe, the structure of the adduct in question has been determined by J. P. DeClercq and G. Germain. Since this structure determination fully confirms the correctness of the formulation of Fuks *et al.*, I am happy to withdraw the reservations I have expressed concerning the mechanism they have proposed.

C. K. BRADSHER

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Meso-ionic Compounds*

W. DAVID OLLIS

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Sheffield, England*

AND CHRISTOPHER A. RAMSDEN

*School of Chemical Sciences, University of East Anglia,
Norwich, England*

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* The review is based on two lectures given by one of us (W.D.O.): a Plenary Lecture entitled "Meso-ionic Heterocycles—Fact and Fiction" given at the Chemical Society Autumn Meeting (September 26, 1972) and the Second Ronald Slack Memorial Lecture, entitled "Meso-ionic Heterocycles—Serendipity and Systematic Investigation" (February 8, 1974).

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I. Introduction

The introduction of the concept of meso-ionic molecules by Baker and Ollis^{1,2} in 1949 has proved to be a fruitful development in heterocyclic chemistry, and many new meso-ionic systems have been reported during the past two decades. These studies have been concerned with the synthesis and general chemistry of meso-ionic heterocycles, but an additional incentive has been provided by the discovery that some meso-ionic compounds participate in 1,3-dipolar cycloaddition reactions.³ These cycloaddition reactions of meso-ionic compounds are of considerable general interest in themselves, and they also provide novel synthetic routes to a large variety of heterocycles. Interest in meso-ionic compounds has also been encouraged by the discovery that some types show various pharmacological activities.⁴

Consideration of the structure of the sydnones (1) led to our proposal of the term meso-ionic.¹ When this term was proposed, it included a number of known heterocycles; the prediction was also made that new representatives of this general class might be discovered. Subsequently the sydnone imines (2) were recognized either as their cations (3) or as their *N*-acyl derivatives (4). The extensive chemistry of the sydnones (1) and the sydnone imines (2) has been well reviewed elsewhere,²⁻⁹ and

¹ W. Baker, W. D. Ollis, and V. D. Poole, *J. Chem. Soc.*, 307 (1949); 1542 (1950).

² W. Baker and W. D. Ollis, (a) *Chem Ind. (London)*, 910 (1955); (b) *Quart. Rev.* 11, 15 (1957).

³ R. Huisgen, (a) *Angew. Chem., Int. Ed. Engl.* 2, 565 (1963); (b) *Chem. Soc. Spec. Publ.* 21, 51 (1967); (c) *Rev. Real Acad. Cienc. Exactas, Fis. Natur. Madrid* 65, 293 (1971) [*CA* 75, 109421n (1971)].

⁴ L. B. Kier and E. B. Roche, *J. Pharm. Sci.* 56, 149 (1967). For discussion of more recent papers and additional references, see later section.

⁵ P. Zuman, *Chem. Listy* 53, 1029 (1959).

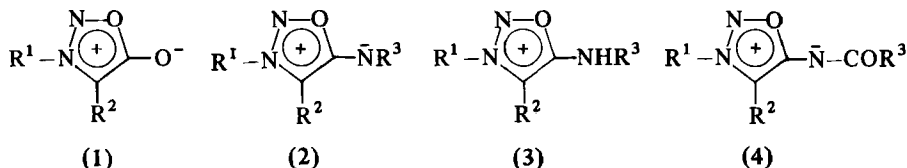
⁶ Y. Noël, *Bull. Soc. Chim. Fr.*, 173 (1964); H. H. Kubbinga, *Chem. Tech. (Amsterdam)* 28, 4 (1973) [*CA* 78, 111165n (1973)].

⁷ F. H. C. Stewart, *Chem. Rev.* 64, 129 (1964).

⁸ N. Suciú, *Stud. Cercet. Chim.* 16, 117 (1968).

⁹ (a) M. Ohta and H. Kato, *Nippon Kagaku Zasshi* 86, 661 (1965) [*CA* 65, 2247h (1966)]; (b) M. Ohta and H. Kato, in "Nonbenzenoid Aromatics" (J. P. Snyder, ed.), pp. 117-248. Academic Press, New York, 1969; (c) M. Ohta, *Yuki Gosei Kagaku Kyokai Shi* 28, 281 (1970) [*CA* 72, 131633t (1970)].

these topics are not given detailed consideration in this review. However, recent work on the sydnones and sydnone imines is included in Sections IX, XI, and XII, which deal with photochemistry, theoretical studies, and pharmacological activity.



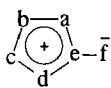
The purpose of the present review is to provide a general survey of meso-ionic heterocycles described up to September 1974. Some more recent references are also included, but in view of the extensive current activity in this area of heterocyclic chemistry, it is necessary to be selective rather than comprehensive. No attempt has been made to discuss the chemistry of meso-ionic heterocycles in detail. Our main objective is to present a summary of the presently known types of meso-ionic heterocycles, which can then be considered in relation to the total number of possibilities associated with certain structural conditions.

It is now evident that it is desirable to divide five-membered meso-ionic heterocycles into two general classes: type A and type B. This review is mainly concerned with the presently known 44 members of type A (Table I) and eight members of type B (Table II). Brief reference is made at the end of the review to various six-membered heterocycles and polycyclic systems that have been described as meso-ionic, but it is now firmly proposed that this practice should be discontinued.

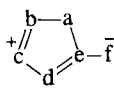
II. The Representation of Meso-ionic Heterocycles

Since its introduction in 1949,¹ the term meso-ionic has found almost universal recognition. Its application has depended upon the definition² that "a compound may be appropriately called meso-ionic if it is a five- or possibly a six-membered heterocyclic compound which cannot be represented *satisfactorily* by any one covalent or polar structure and possesses a sextet of electrons in association with the atoms comprising the ring. The ring bears a fractional positive charge balanced by a corresponding negative charge located on a covalently attached atom or group of atoms." When this definition was proposed,² it was recognized that an inevitable ambiguity was associated with the word "satisfactorily." The adoption of the term meso-ionic and its frequent use in accord with the above definition has demonstrated its usefulness.

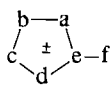
However, several symbols involving positive and negative signs continue to be used. These are shown in the general type formulas (5–8), in which a, b, c, d, e, and f refer to atoms or groups derived from suitably substituted carbon- or heteroatoms. The arguments in favor of the use of the large, full circle¹⁰ as in formula 5 to represent delocalization in association with a partial positive charge have been clearly presented.¹⁰ These arguments were subsequently reinforced by a general policy adopted by the Chemical Society for the structural representation of aromatic compounds.¹⁰ Because meso-ionic heterocycles cannot be represented by a covalent formulation, the use of the symbolism 5 is still advocated; 5 is preferred to 6, 7, or 8. This symbolism (5) is intended to convey the general attributes of their structure and electronic makeup so that the five-membered heterocyclic ring is associated with a partial positive charge and the exocyclic substituent bears a corresponding partial negative charge. It is incorrect to conclude that the general formula 5 necessarily implies extensive polarization or the exhibition of proper-



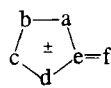
(5)



(6)



(7)



(8)

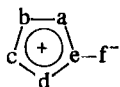
ties or stability that can be characteristically associated with classical aromaticity.

The betaine-type formula (6) has not been found to be acceptable for the general representation of meso-ionic heterocycles, but in view of the recent advocacy^{9b} of the \pm symbolism depicted in formula 7 some further comment is necessary. Although we originally used this \pm symbolism in the representation of the sydnones, we subsequently recommended² its replacement by 5 because this is in accord with current practice.¹⁰ Our present view is that the use of a special \pm symbol (7) is not justified: it is too vague to be useful, and in any case it can cause misunderstanding if formulas of type 8 with $e=f$ are used as well as those of type 7 with $e=f$. The general formula 5 has much to commend it for discussion of type A and type B five-membered meso-ionic heterocycles and for the correlation of corresponding structural features of these two types (Tables I and II).

¹⁰ W. Baker, *Proc. Chem. Soc.*, 75 (1959); in "Perspectives in Organic Chemistry" (Sir Alexander Todd, ed.), pp. 28–67. Interscience, New York, 1956.

TABLE I

KNOWN FIVE-MEMBERED MESO-IONIC HETEROCYCLES OF TYPE A (19)



Parent system	Hetero- cycle	Atom or group ^a					
		a	b	c	d	e	f
Oxazoles							
1,3-Oxazol-5-ones	66	O	CR	NR	CR	C	O
1,3-Oxazol-5-imines	80	O	CR	NR	CR	C	NR
1,3-Oxazol-4-imines	87	NR	CR	O	CR	C	NR
Diazoles							
1,3-Diazol-4-ones	91	NR	CR	NR	CR	C	O
1,3-Diazol-4-imines	98	NR	CR	NR	CR	C	NR
1,3-Diazole-4-thiones	103	NR	CR	NR	CR	C	S
Thiazoles							
1,3-Thiazol-5-ones	105	S	CR	NR	CR	C	O
1,3-Thiazol-5-imines	108	S	CR	NR	CR	C	NR
1,3-Thiazole-5-thiones	109	S	CR	NR	CR	C	S
1,3-Thiazol-4-ones	114	NR	CR	S	CR	C	O
1,3-Thiazol-4-imines	124	NR	CR	S	CR	C	NR
Dithioles							
1,3-Dithiol-4-ones	134	S	CR	S	CR	C	O
1,3-Dithiol-4-imines	141	S	CR	S	CR	C	NR
Oxadiazoles							
1,3,4-Oxadiazol-2-ones	146	O	CR	NR	N	C	O
1,3,4-Oxadiazol-2-imines	153	O	CR	NR	N	C	NR
1,3,4-Oxadiazole-2-thiones	156	O	CR	NR	N	C	S
1,3,4-Oxadiazol-2-enes	164	O	CR	NR	N	C	CXY ^b
1,2,3-Oxadiazol-5-ones	1	O	N	NR	CR	C	O
1,2,3-Oxadiazol-5-imines	2	O	N	NR	CR	C	NR
Oxathiazoles							
1,3,2-Oxathiazol-5-ones	169	O	N	S	CR	C	O
Triazoles							
1,2,3-Triazol-4-ones	176	NR	N	NR	CR	C	O
1,2,3-Triazol-4-imines	193	NR	N	NR	CR	C	NR
1,2,3-Triazole-4-thiones	196	NR	N	NR	CR	C	S
1,2,4-Triazol-3-ones	200	NR	CR	NR	N	C	O
1,2,4-Triazol-3-imines	216	NR	CR	NR	N	C	NR ^c
1,2,4-Triazole-3-thiones	227	NR	CR	NR	N	C	S
1,2,4-Triazol-3-enes	240	NR	CR	NR	N	C	CXY ^b
Thiadiazoles							
1,3,4-Thiadiazol-2-ones	243	S	CR	NR	N	C	O
1,3,4-Thiadiazol-2-imines	247	S	CR	NR	N	C	NR ^c
1,3,4-Thiadiazole-2-thiones	251	S	CR	NR	N	C	S
1,3,4-Thiadiazol-2-enes	261	S	CR	NR	N	C	CXY ^b
1,2,3-Thiadiazol-4-ones	265	NR	N	S	CR	C	O
1,2,4-Thiadiazol-3-imines	268	NR	CR	S	N	C	NR

TABLE I—continued

Parent system	Hetero- cycle	Atom or group ^a					
		a	b	c	d	e	f
Oxatriazoles							
1,2,3,4-Oxatriazol-5-ones	271	O	N	NR	N	C	O
1,2,3,4-Oxatriazol-5-imines	277	O	N	NR	N	C	NR
1,2,3,4-Oxatriazole-5-thiones	286	O	N	NR	N	C	S
Tetrazoles							
1,2,3,4-Tetrazol-5-ones	289	NR	N	NR	N	C	O
1,2,3,4-Tetrazol-5-imines	293	NR	N	NR	N	C	NR
1,2,3,4-Tetrazole-5-thiones	295	NR	N	NR	N	C	S
1,2,3,4-Tetrazol-5-enes	296	NR	N	NR	N	C	CXY ^b
Thiatriazoles							
1,2,3,4-Thiatriazol-5-ones	297	S	N	NR	N	C	O
1,2,3,4-Thiatriazol-5-imines	299	S	N	NR	N	C	NR
1,2,3,4-Thiatriazole-5-thiones	300	S	N	NR	N	C	S
1,2,3,4-Thiatriazol-5-enes	301	S	N	NR	N	C	CXY ^b

^aThe groupings a and c each contribute 2 electrons to the π -electron system of the hetero-cycle; b, d, e, and f each contribute 1 electron.

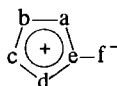
^bIn these compounds the group f is a stabilized carbanionoid residue. The substituents X and Y include CO₂Et, CN, or a fluorenylidene residue.

^cRecently these two classes have been extended to include cases where R is N=CHAr.

Thus, the stabilized carbanionoid residue f is associated with the grouping $\overline{\text{N-N-CHAr}}$.

TABLE II

KNOWN FIVE-MEMBERED MESO-IONIC HETEROCYCLES OF TYPE B (20)



Parent system	Hetero- cycle	Atom or group ^a					
		a	b	c	d	e	f
Oxazoles							
1,2-Oxazol-4-imines	370	CR	O	NR	CR	C	NR
Diazoles							
1,2-Diazol-4-ones	373	CR	NR	NR	CR	C	O
1,2-Diazol-4-imines	382	CR	NR	NR	CR	C	NR
Thiazoles							
1,2-Thiazol-4-imines	386	CR	S	NR	CR	C	NR
Dithioles							
1,2-Dithiol-4-ones	388	CR	S	S	CR	C	O
Tetrazoles							
1,2,3,4-Tetrazol-5-ones	392	N	NR	NR	N	C	O
1,2,3,4-Tetrazol-5-imines	399	N	NR	NR	N	C	NR
1,2,3,4-Tetrazole-5-thiones	413	N	NR	NR	N	C	S

^aThe groupings b and c each contribute 2 electrons to the π -electron system of the hetero-cycle; a, d, e, and f each contribute 1 electron.

III. The Two Types of Five-Membered Meso-ionic Heterocycles

Six general types (Fig. 1) of five-membered heterocycles can be depicted (9–14) in which a, b, c, d, e, and f represent suitably substituted carbon or heteroatoms. These are chosen to permit a mutually conjugated system associated with all the component atoms of the five-membered ring as well as the exocyclic substituent. The conjugated systems are associated with eight π -electrons whose origin is indicated by superscripts (see 9–14). Each of these representations (9–14) is then developed, giving the corresponding formulas (15–20).

The six general heterocyclic types (15–20) in association with the examples (21–27) illustrate particularly well the need for the term meso-ionic and the requirements that should be observed in meeting the condition of *satisfactory representation*. The compounds 21¹¹ and 22¹² are certainly acceptably represented by their covalent formulations. The types 17 and 18 correspond with the *N*-oxides 23¹³ and 24,¹⁴ and these are also satisfactorily represented by the single dipolar structures 23 and 24. Similarly, the compounds 25 are not meso-ionic; they are acceptably described by dipolar structures of the general type 18.^{3a} Compounds belonging to the general types 19^{14a} and 20^{14a} cannot be satisfactorily represented by covalent or single dipolar structures, and they are best regarded as five-membered meso-ionic heterocycles. It is convenient to associate the two general formulas 19 and 20 with type A and type B meso-ionic systems. The origin of the π -electron system of type A meso-ionic compounds is given in the cipher 13, and they are exemplified by the sydnones (26). The origin (14) of the electrons constituting the π -electron system of type B meso-ionic compounds (20) is different; this class is exemplified by dehydrodithizone (27, R = Ph).

For the five-membered heterocycles (Fig. 1), it is important that the term meso-ionic is reserved for members of the general types 19 and 20. This point needs to be emphasized because recently several structures have been described as meso-ionic although they were in fact ylides 17 and 18. Petersen and Heitzer¹⁵ have referred to the intermediate isolated

¹¹ A. J. Boulton and A. R. Katritzky, *Tetrahedron* 12, 41 (1961).

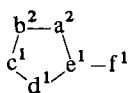
¹² A. Hetzheim and K. Möckel, *Advan. Heterocyc. Chem.* 7, 193 (1966).

¹³ A. R. Katritzky and J. M. Lagowski, "Chemistry of the Heterocyclic N-Oxides," Academic Press, New York, 1971; E. Ochiai, "Aromatic Amine Oxides," Elsevier, Amsterdam, 1967.

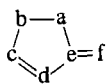
¹⁴ L. B. Volodarsky, A. N. Lisack, and V. A. Koptuyg, *Tetrahedron Lett.*, 1565 (1965).

^{14a} Inspection of Fig. shows that the formulas 19 and 20 as printed are identical. A difference becomes apparent only when they are considered in relation to the corresponding formulas (13 and 14), which indicate the origin of the electrons associated with their π -systems.

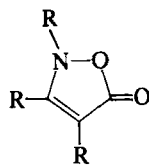
¹⁵ S. Petersen and H. Heitzer, *Angew. Chem., Int. Ed. Engl.* 9, 67 (1970).



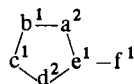
(9)



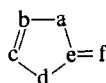
(15)



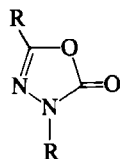
(21)



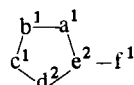
(10)



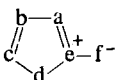
(16)



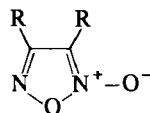
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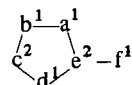
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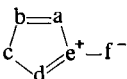
(17)



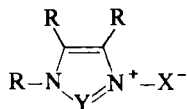
(23)



(12)

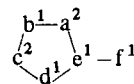


(18)

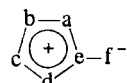


(24) X = O; Y = CR

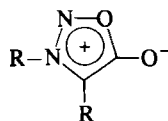
(25) X = NR; Y = N



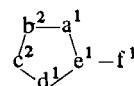
(13)



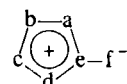
(19)



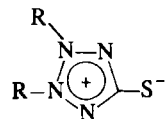
(26)



(14)



(20)



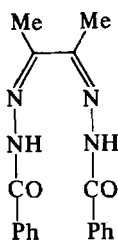
(27)

FIG. 1. Six general types of five-membered heterocycles (9-14), with examples.

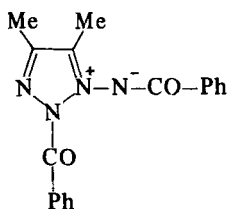
by the oxidation of butane-2,3-dione bisbenzoylhydrazone (28) as the "meso-ionic" compound 29, whereas this structure (29) belongs to the ylide class (17). Further investigation¹⁶ has established that this isolable intermediate is in fact the amidotriazole enol benzoate (30). The

¹⁶ H. Bauer, A. J. Boulton, W. Fedeli, A. R. Katritzky, A. Majid-Hamid, F. Mazza, and A. Vaciago, *Angew. Chem., Int. Ed. Engl.* **10**, 129 (1971).

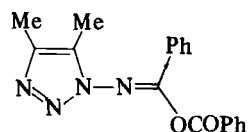
postulated intermediate in the thermal and photochemical transformation of bisphenylazostilbene (31) into 2,4,5-triphenyl-1,2,3-triazole (32) has been called "meso-ionic,"^{17a} whereas it should have been described as an ylide (33) since it belongs to the general class 17. Another example of incorrect terminology is the description of the adducts of dicyanoketene ethylene acetals with pyridine thioamides and sulfides as "meso-ionic."^{17b} This is not correct since these adducts are acceptably described as enol betaines. Some benztriazole *N*-oxides have also been incorrectly described as "meso-ionic";^{17c} this is unnecessary since they clearly belong to the ylide general class (17). The use of the term "meso-



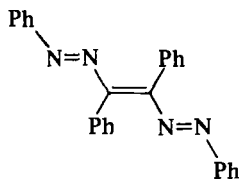
(28)



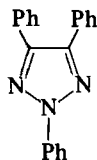
(29)



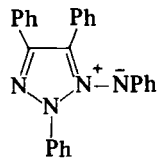
(30)



(31)



(32)



(33)

ionic zwitterion"^{17a} cannot be recommended. An amusingly confused situation has been provided by a recent abstract. The term "meso-ionic" does not appear in the report of the crystal structure of two *N*-ammonia amidates^{17e} and neither does it appear in the abstract.^{17f} However, this abstract is indexed under "meso-ionic ammonium crystal structure"^{17g}

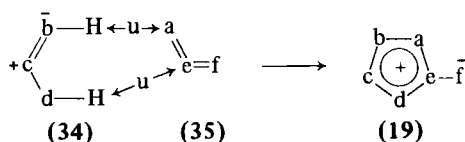
Having emphasized the need to discriminate between the ylides 17 and 18 and the five-membered meso-ionic heterocycles 19 and 20, it is

¹⁷ (a) C. S. Angadiyavar, K. B. Sukumaran, and M. V. George, *Tetrahedron Lett.*, 633 (1971); (b) W. J. Middleton and V. A. Engelhardt, *J. Amer. Chem. Soc.* **80**, 2788 (1958); (c) D. F. Hayman, G. B. Jackman, V. Petrow, O. Stephenson, and A. M. Wild, *J. Pharm. Pharmacol.* **16**, 677 (1964); (d) H. E. Zimmerman, *Angew. Chem., Int. Ed. Engl.* **8**, 1 (1969); (e) A. F. Cameron, N. J. Hair, D. G. Morris, and D. M. Hawley, *Chem. Commun.*, 725 (1971); (f) *CA* **75**, 81352q (1971); (g) *CA* **75**, 54K (1971).

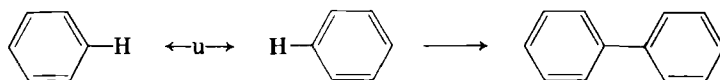
necessary to mention that the systematic naming of meso-ionic compounds is best done using the same nomenclature as that used to name betaines. Thus, *NC*-diphenylsydnone (26, $R = Ph$) may be systematically described as anhydro-5-hydroxy-3,4-diphenyl-1,2,3-oxadiazolium hydroxide. However, this nomenclature is somewhat cumbersome, so it is often convenient to refer to the various types of meso-ionic compounds in terms of the parent heterocyclic system and then qualify such names by the adjective meso-ionic. Thus, the sydnone (26) are conveniently described as meso-ionic 1,2,3-oxadiazol-5-ones. This terminology is frequently used throughout this review, and the relation between structural formulae and names is given in Tables I and II.

IV. Five-Membered Meso-ionic Heterocycles of Type A

Forty-four five-membered heterocycles of type A (13, 19) have been described (Table I). If the atoms or groups a, b, c, d, e, and f are selected from suitably substituted carbon, nitrogen, oxygen, and sulfur atoms, then with these conditions it can be shown that 144 structural possibilities are provided by the general formula 19. The number of structural possibilities can be deduced in various ways, but a very useful approach is to regard type A meso-ionic molecules (19) as being derived by the *union* ($\leftarrow u \rightarrow$) of 1,3-dipoles (34) and heterocumulenes (35).



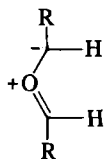
In this approach, the term *union* is used in the sense defined by Dewar:¹⁸ *union* is a process in which two conjugated molecules combine in such a way that their two π -systems unite into one larger one. For example, biphenyl can be formed by the *union* of two molecules of benzene:



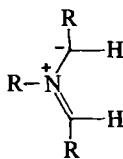
The conditions given above for a, b, c, d, e, and f provide nine 1,3-dipoles (36–44), which can be involved in union with ten heterocumulenes ($e = C$; a and f variously chosen from $> O$, $> S$,

¹⁸ M. J. S. Dewar, "The Molecular Orbital Theory of Organic Chemistry," p. 194. McGraw-Hill, New York, 1969.

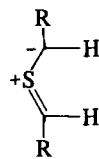
> NR, and > CXY). This provides 144 structural possibilities, of which 44 are at present known (Table I).



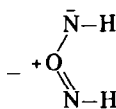
(36) Carbonyl ylides



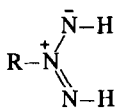
(37) Azomethine ylides



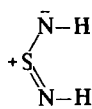
(38) Thiocarbonyl ylides



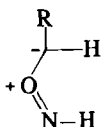
(39) Nitrosoimines



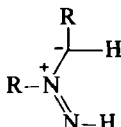
(40) Azonium imines



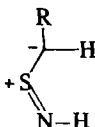
(41) Thionitrosoimines



(42) Carbonyl imines



(43) Azomethine imines



(44) Thiocarbonyl imines

The relation between the structures of the 44 known five-membered meso-ionic heterocycles (Table I) and the 1,3-dipoles (36–44) from which they can be formally derived by *union* is as follows:

(36) Carbonyl ylides:	87
(37) Azomethine ylides:	66, 80, 91, 98, 103, 105, 108, 109
(38) Thiocarbonyl ylides:	114, 124, 134, 141
(40) Azonium imines:	271, 277, 286, 289, 292, 294, 296, 297, 299, 300, 301
(43) Azomethine imines:	1, 2, 146, 153, 156, 164, 176, 193, 196, 200, 216, 227, 240, 243, 247, 251, 261
(44) Thiocarbonyl imines:	169, 265, 268

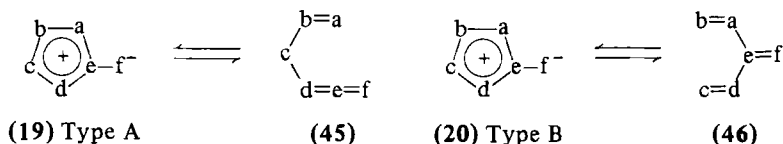
This list shows that the five-membered meso-ionic heterocycles related to the azomethine imine 1,3-dipole (43) comprise the largest group and that meso-ionic compounds related to the nitrosoimines (39), thionitrosoimines (41), and carbonyl imines (42) are not yet known. Clearly synthetic challenges still exist in the field of meso-ionic compounds.

V. Five-Membered Meso-ionic Heterocycles of Type B

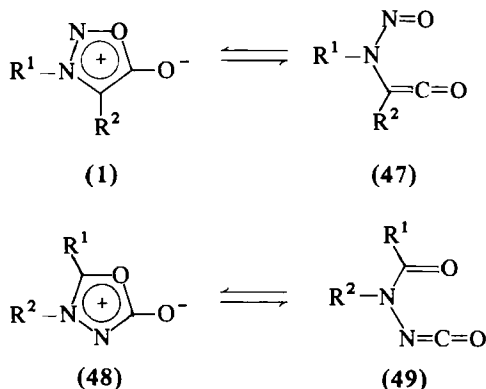
This second class of five-membered heterocyclic meso-ionic compounds is represented by the type formula **14**; **20**. So far, only eight representatives (Table II) of type B have been described, whereas acceptable combinations of the groupings a, b, c, d, e, and f derived from suitably substituted carbon, nitrogen, oxygen, or sulfur atoms lead, in principle, to 84 possibilities. However, not all these 84 possible structures are necessarily well based because valence tautomerism (see Section VI) might well be associated with thermodynamic preference for the acyclic covalent valence isomer (**46**) rather than the cyclic meso-ionic alternative (**20**).

VI. The Valence Tautomerism of Five-Membered Meso-ionic Compounds of Type A and Type B

This possibility can be depicted generally by the situations **19** \rightleftharpoons **45** for type A and **20** \rightleftharpoons **46** for type B five-membered meso-ionic heterocycles.

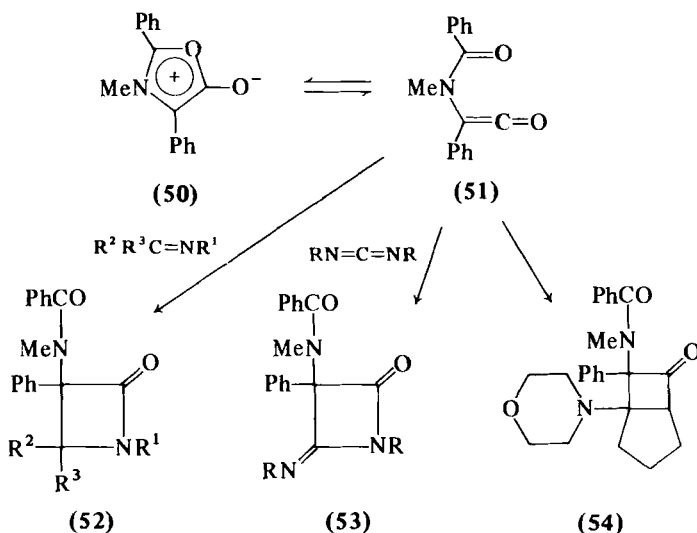


For the type A meso-ionic heterocycles the valence tautomerism **19** \rightleftharpoons **45** is now considered. Examples include the possibility that the sydnones (**1**) could be associated with a valence tautomerism involving the nitrosoketene isomer (**47**).^{1,2} Similarly, the relation between the isosydnone (**48**) and their acylaminoisocyanate isomers (**49**) have been



noted.¹⁹ Although there is no definitive evidence that the sydrones (1) are involved in the valence tautomerism $1 \rightleftharpoons 47$, some cycloaddition reaction of isosydrones (48) have been considered as involving the acylaminoisocyanate (49).²⁰

Some highly relevant results have been obtained with the meso-ionic 1,3-oxazol-5-one (50), whose cycloaddition reactions are most directly interpreted^{3,21} as involving the valence tautomer 51. Thus, azomethines gave azetidinones (52), carbodiimides gave iminoazetidones (53), and enamines [e.g., *N*-(1-cyclopentenyl)morpholine] gave the intermediate cycloadducts (e.g., 54) which are then transformed to the products (e.g., 55; this product is incorrectly formulated in a review^{9b}). The 1,3-oxazol-5-one (50) on heating in xylene gives the allene (57), which is probably formed from the dimer (56) of the valence tautomer (51). The probable involvement of the acylaminoketene (51) as a valence tautomer in these thermal reactions is clear, but its spectroscopic detection was not achieved: presumably its equilibrium concentration must be very small. In contrast the valence tautomer (59) has been detected spectroscopically (ν_{\max} 2260 cm^{-1} ; $\text{N}=\text{C}=\text{O}$) during the photolysis of the meso-ionic 1,3,4-thiadiazol-2-one (58).²²



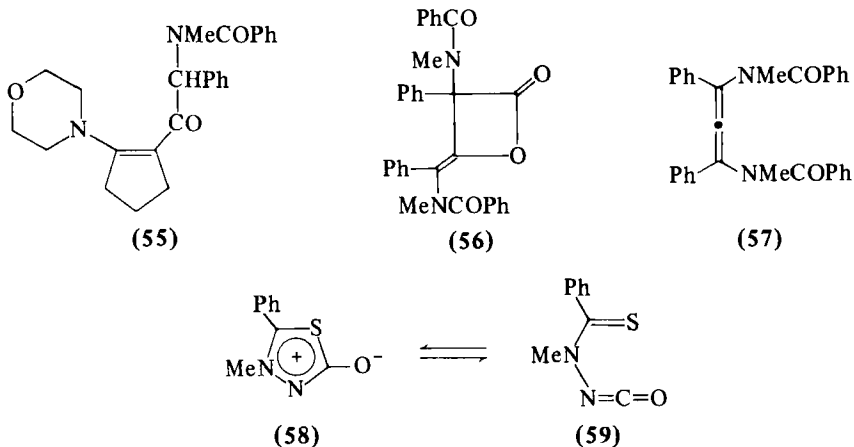
¹⁹ (a) A. R. McCarthy, W. D. Ollis, A. N. M. Barnes, L. E. Sutton, and C. Ainsworth, *J. Chem. Soc. B*, 1185 (1969); (b) P. B. Talukdar, S. K. Sengupta, and A. K. Datta, *J. Indian Chem. Soc.* **48**, 591 (1971).

²⁰ A. R. McCarthy, W. D. Ollis, and C. A. Ramsden, *J. Chem. Soc., Perkin Trans. I*, 624 (1974).

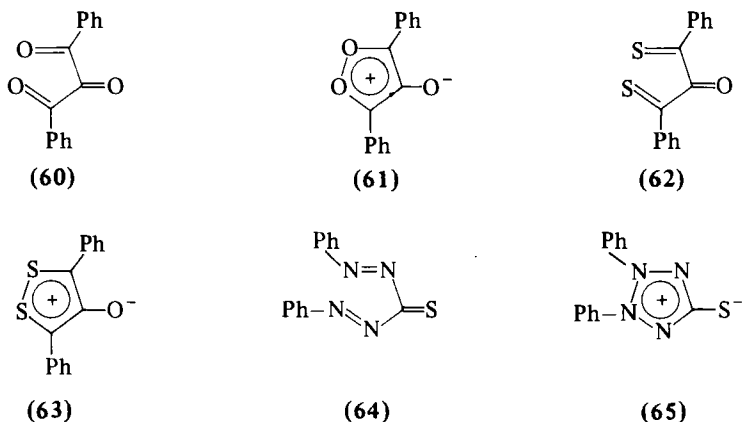
²¹ R. Huisgen, E. Funke, F. C. Schaefer, and R. Knorr, *Angew. Chem., Ed. Engl.* **6**, 367 (1967); E. Funke and R. Huisgen, *Chem. Ber.* **104**, 3222 (1971).

²² R. M. Moriarty, R. Mukherjee, O. L. Chapman, and D. R. Eckroth, *Tetrahedron Lett.*, 397 (1971).

Regarding the valence tautomerism $20 \rightleftharpoons 46$, which is, in principle, possible for five-membered meso-ionic heterocycles of type B, it may be noted that whereas the triketone (60) is obviously the more stable



partner with respect to its meso-ionic valence tautomer (61), the converse situation exists in the case of the bisthiotriketone (62). This has the meso-ionic 1,2-dithiol-4-one structure (63).^{23,24} Similarly, dehydrodithizone has the meso-ionic structure 65^{25,26} rather than the covalent alternative 64.



²³ K. Inouye, S. Sato, and M. Ohta, *Bull. Chem. Soc. Jap.* **43**, 1911 (1970).

²⁴ A. Schönberg and E. Frese, *Tetrahedron Lett.*, 4063 (1969); *Chem. Ber.* **103**, 3885 (1970).

²⁵ E. Fischer and E. Besthorn, *Ann.* **212**, 316 (1882).

²⁶ R. S. Ramakrishna and H. M. N. H. Irving, *Chem. Commun.*, 1356 (1969).

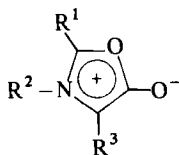
VII. The Chemistry of Meso-ionic Compounds of Type A

These are listed under the parent heterocyclic systems in the order given in Table I (Section IV).

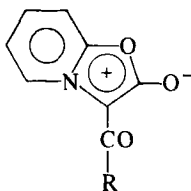
A. OXAZOLES

1. 1,3-Oxazol-5-ones (Anhydro-5-hydroxy-1,3-oxazolium Hydroxides) (66)

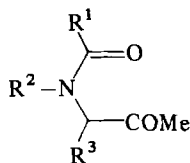
Anhydro-acylation of 1,2-dihydro-2-oxo-1-pyridylacetic acid with acid anhydrides yields bicyclic meso-ionic 4-acyl-1,3-oxazol-5-ones (67).^{27,28} Huisgen and his co-workers have reported^{3,21,29,30} extensive studies of the monocyclic meso-ionic 1,3-oxazol-5-ones (66), which they have lightheartedly named *münchnones*.³ Cyclodehydration of *N*-benzoyl-*N*-methyl-*C*-phenylglycine using acetic anhydride at 55° gives the 3-methyl-2,4-diphenyl derivative (66, R¹ = R³ = Ph; R² = Me) as orange-yellow needles, m.p. 151°–152° (decomp.). This compound is very reactive:³⁰ exposure to moist air gives back the acylamino acid, alcoholysis yields the ester, and aminolysis the amide. The meso-ionic oxazolone (66, R¹ = R³ = Ph; R² = Me) reacts with acetic anhydride at 90° giving the methyl ketone (68, R¹ = R³ = Ph; R² = Me) directly. Based upon this result, a mechanism for the Dakin–West reaction involving a meso-ionic intermediate has been proposed.³¹



(66)



(67)



(68)

N-Benzoyl-*C*-phenylglycine with trifluoroacetic anhydride at room temperature yields the bright yellow 4-trifluoroacetyl-1,3-oxazol-5-one (66, R¹ = R² = Ph; R³ = COCF₃), but the corresponding reaction with

²⁷ A. Lawson and D. H. Miles, *Chem. Ind. (London)*, 461 (1958).

²⁸ A. Lawson and D. H. Miles, *J. Chem. Soc.*, 2865 (1959); 1945 (1960).

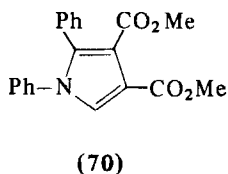
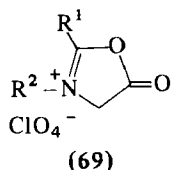
²⁹ R. Huisgen, H. Gotthardt, H. O. Bayer, and F. C. Schaefer, *Angew. Chem., Ed. Engl.* **3**, 136 (1964).

³⁰ H. O. Bayer, R. Huisgen, R. Knorr, and F. C. Schaefer, *Chem. Ber.* **103**, 2581 (1970).

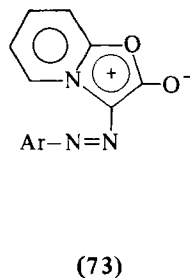
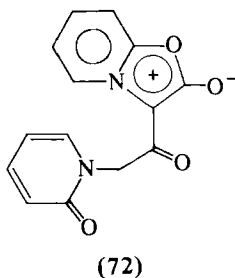
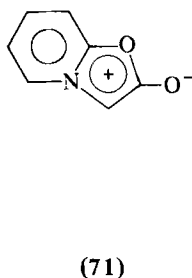
³¹ R. Knorr and R. Huisgen, *Chem. Ber.* **103**, 2598 (1970).

acetic anhydride gave the Dakin-West reaction product (**68**, $R^1 = R^2 = \text{Ph}$; $R^3 = \text{H}$).³² Other cyclodehydrating agents used to prepare meso-ionic 1,3-oxazol-5-ones (**66**) include oxalyl chloride^{33,34} or dicyclohexylcarbodiimide.³⁵

N-Alkyl- and *N*-aryl- α -acylamino acids with a mixture of acetic anhydride and perchloric acid form 1,3-oxazolonium perchlorates



(**69**),³⁶ which with trifluoroacetic anhydride and base (triethylamine or solid sodium carbonate) yield the known 4-trifluoroacetyl derivative of the meso-ionic 1,3-oxazol-5-one (**66**, $R^3 = \text{COCF}_3$). The 4-unsubstituted meso-ionic 1,3-oxazol-5-ones (**66**, $R^3 = \text{H}$) could not be isolated, but treatment of the 1,3-oxazolonium perchlorate (**69**, $R^1 = R^2 = \text{Ph}$) with base and dimethyl acetylenedicarboxylate gave the pyrrole (**70**), presumably by 1,3-cycloaddition to the meso-ionic 1,3-oxazol-5-one (**66**, $R^1 = R^2 = \text{Ph}$; $R^3 = \text{H}$).³⁶



Cyclodehydration of 1-carboxymethyl-2-pyridone with acetic anhydride and perchloric acid gave the corresponding 1,3-oxazolonium perchlorate which with triethylamine gave the dimer (**72**) directly. Similar dimerization of other meso-ionic 1,3-oxazol-5-ones (**66**) have been reported.³⁶ The monomer (**71**) could not be isolated, but acetyl (**67**, $R = \text{Me}$) and benzoyl (**67**, $R = \text{Ph}$) derivatives were prepared from a

³² G. Singh and S. Singh, *Tetrahedron Lett.*, 3789 (1964).

³³ W. D. Burrows, *J. Org. Chem.* **31**, 3435 (1966).

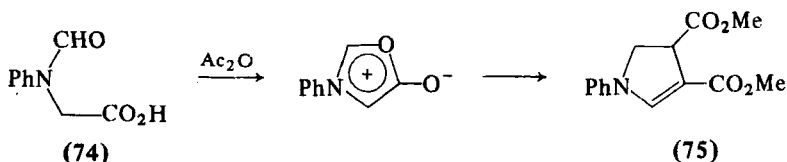
³⁴ M. Ohta and T. Mase, *Nippon Kagaku Zasshi* **89**, 714 (1968); [*CA* **70**, 11603v (1969)].

³⁵ C. V. Greco, R. P. Gray, and V. G. Grosso, *J. Org. Chem.* **32**, 4101 (1967).

³⁶ G. V. Boyd, *Chem. Commun.*, 1410 (1968); G. V. Boyd and P. H. Wright, *J. Chem. Soc., Perkin Trans. I*, 909, 914 (1972).

solution of the monomer (71). Treatment of the monomer solution with aryldiazonium fluoroborates gave the azo derivatives (73).^{37,38}

The meso-ionic 1,3-oxazol-5-ones show an incredible array of cycloaddition reactions. Reference has already been made to the cycloaddition reactions of the derivative 50, which are interpreted as involving cycloaddition to the valence tautomer 51.²¹ In addition, an extremely comprehensive study of the 1,3-dipolar cycloaddition reactions of meso-ionic 1,3-oxazol-5-ones (66) has been undertaken by Huisgen and his co-workers.^{3,39-45} The 1,3-dipolarophiles that have been examined include alkenes, alkynes, aldehydes, α -keto esters, α -diketones, thiobenzophenone, thiono esters, carbon oxysulfide, carbon disulfide, nitriles, nitro-, nitroso-, and azo-compounds, and cyclopropene and cyclobutene derivatives.⁴⁶ In these reactions the 1,3-oxazol-5-ones (66)



may be generated in the presence of the 1,3-dipolarophile,⁴⁶ and an example³ of this *in situ* technique is the direct formation of the 2-pyrroline (75) in the reaction of *N*-formyl-*N*-phenylglycine (74) with acetic anhydride and dimethyl fumarate.

These results are relevant to the tautomerism which is, in principle, possible between Δ^2 -oxazolin-5-ones (azlactones) (76) and their meso-ionic isomers (77). Kille and Fleury⁴⁷ interpreted the spectroscopic

³⁷ G. V. Boyd and P. H. Wright, *Chem. Commun.*, 182 (1969).

³⁸ G. V. Boyd and P. H. Wright, *J. Chem. Soc. C*, 1485 (1970); G. V. Boyd, in "Aromaticity, Pseudo-aromaticity, Anti-aromaticity" (E. D. Bergmann and B. Pullman, eds.), p. 166. Israel Acad. Sci. Humanities, Jerusalem, 1971.

³⁹ H. Gotthardt, R. Huisgen, and F. C. Schaefer, *Tetrahedron Lett.*, 487 (1964).

⁴⁰ R. Huisgen, H. Gotthardt, H. O. Bayer, and F. C. Schaefer, *Chem. Ber.* **103**, 2611 (1970).

⁴¹ H. Gotthardt and R. Huisgen, *Chem. Ber.* **103**, 2625 (1970).

⁴² R. Knorr, R. Huisgen, and G. K. Staudinger, *Chem. Ber.* **103**, 2639 (1970).

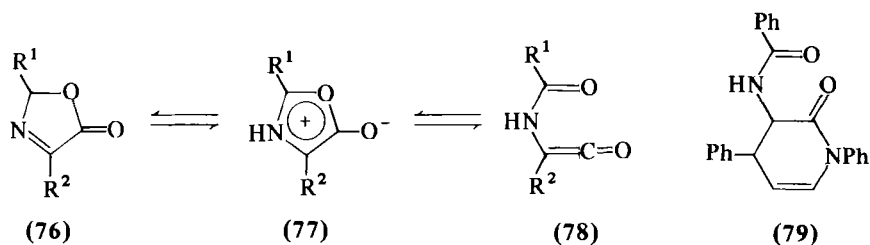
⁴³ R. Huisgen, E. Funke, H. Gotthardt, and H.-L. Panke, *Chem. Ber.* **104**, 1532 (1971).

⁴⁴ E. Funke, R. Huisgen, and F. C. Schaefer, *Chem. Ber.* **104**, 1550 (1971).

⁴⁵ E. Brunn, E. Funke, H. Gotthardt, and R. Huisgen, *Chem. Ber.* **104**, 1562 (1971).

⁴⁶ (a) K. T. Potts and U. P. Singh, *Chem. Commun.*, 66 (1969); (b) K. T. Potts and D. McKeough, *J. Amer. Chem. Soc.* **95**, 2749 (1973); (c) K. T. Potts and J. Baum, *J. Chem. Soc., Chem. Commun.*, 833 (1973); (d) H. Matsukubo and H. Kato, *ibid.*, 412 (1974); *J. Chem. Soc., Perkin Trans. I*, 632 (1975); T. Eicher and V. Schäfer, *Tetrahedron* **30**, 4025 (1974); (e) H.-D. Martin and M. Hekman, *Angew. Chem., Ed. Engl.* **11**, 926 (1972).

⁴⁷ G. Kille and J.-P. Fleury, *Bull. Soc. Chim. Fr.*, 4636 (1968).



properties of the copper-red anhydro derivative (77, R¹ = Ph; R² = *p*-O₂N . C₆H₄) as supporting the meso-ionic structure (77). Huisgen and his co-workers⁴⁸ have examined the solvent dependence for the equilibrium 76 ⇌ 77, R¹ = R² = Ph, and have given the following estimates of the equilibrium concentration of the meso-ionic partner (77, R¹ = R² = Ph): dimethylformamide 49%, dimethyl sulfoxide 32%, acetone 0.26%, chloroform 0.007%. They have also shown that azlactones 76 ⇌ 77 participate in 1,3-dipolar cycloaddition with alkynes^{49,50} and alkenes.⁵⁰ In view of the extensive earlier studies of azlactones (76), it is remarkable that their tautomerism with meso-ionic 1,3-oxazol-5-ones (77) should have been recognized so recently. It is clear that this tautomerism (76 ⇌ 77) may well be involved in the racemization of optically active amino acids during *N*-acylation.

Recently a novel reaction between the azlactone 76, R¹ = Ph; R² = Me, and cinnamylidene aniline yielding the adduct 79 has been described.^{51a} This result has been interpreted as involving a Diels-Alder cycloaddition between cinnamylidene aniline and the valence tautomeric ketene 78, R¹ = Ph; R² = Me.

The cycloaddition reactions of 2-phenyloxazol-4(5*H*)-one with acetylenic dipolarophiles has been briefly reported.^{51b} The formation of 2-phenylfurans may well involve a tautomerism analogous to that exhibited by azlactones (76 ⇌ 77).

2. 1,3-Oxazol-5-imines (Anhydro-5-amino-1,3-oxazolium Hydroxides) (80)

A mechanism has been proposed⁵² involving a meso-ionic 1,3-oxazol-5-imine (münchnone imine) intermediate for the acid-catalyzed forma-

⁴⁸ H. Gotthardt, R. Huisgen, and H. O. Bayer, *J. Amer. Chem. Soc.* **92**, 4340 (1970).

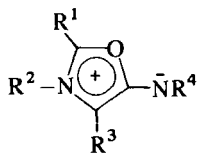
⁴⁹ H. O. Bayer, H. Gotthardt, and R. Huisgen, *Chem. Ber.* **103**, 2356 (1970).

⁵⁰ R. Huisgen, H. Gotthardt, and H. O. Bayer, *Chem. Ber.* **103**, 2368 (1970).

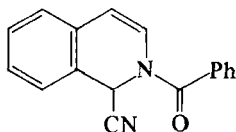
⁵¹ (a) S. Mohan, B. Kumar, and J. S. Sandhu, *Chem. Ind. (London)*, 671 (1971); (b) K. T. Potts and J. Marshall, *J. Chem. Soc. Chem. Commun.*, 1000 (1972).

⁵² R. L. Cobb and W. E. McEwen, *J. Amer. Chem. Soc.* **77**, 5042 (1955).

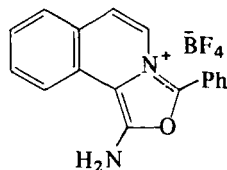
tion of aldehydes from Reissert compounds. Subsequently⁵³ this meso-ionic intermediate was trapped using 1,3-dipolarophiles. 2-Benzoyl-1,2-dihydroisoquinaldonitrile (**81**) and tetrafluoroboric acid gave the Reissert salt (**82**), which with dimethyl acetylenedicarboxylate gave the product **83**, $R^1 = R^2 = \text{CO}_2\text{Me}$, and with ethyl phenyl propiolate yielded the primary adduct (**84**) and a secondary product (**83**, $R^1 = \text{CO}_2\text{Et}$; $R^2 = \text{Ph}$).



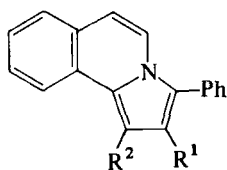
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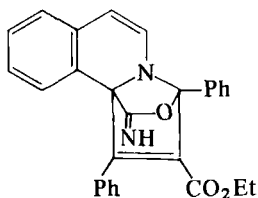
(81)



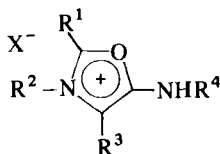
(82)



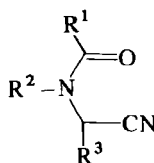
(83)



(84)



(85)



(86)

The 1,3-oxazolium chloride (**85**, $R^1 = R^2 = \text{Ph}$; $R^3 = R^4 = \text{H}$; $\text{X} = \text{Cl}$) is formed from *N*-benzoylanilinoacetonitrile (**86**, $R^1 = R^2 = \text{Ph}$; $R^3 = \text{H}$) and hydrogen chloride.⁵⁴ Similarly, this nitrile (**86**, $R^1 = R^2 = \text{Ph}$; $R^3 = \text{H}$) and acetyl or benzoyl perchlorate give the 1,3-oxazolium perchlorates (**85**, $R^1 = R^2 = \text{Ph}$; $R^3 = \text{H}$; $R^4 = \text{MeCO}$ or $\text{Ph} \cdot \text{CO}$; $\text{X} = \text{ClO}_4$),⁵⁴ but nitriles (**86**) and acid anhydrides give meso-ionic 1,3-oxazol-5-imines (**80**, $R^4 = \text{RCO}$) directly.^{55,56}

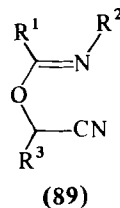
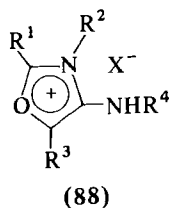
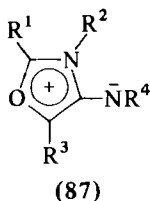
⁵³ W. E. McEwen, I. C. Mineo, Y. H. Shen, and G. Y. Han, *Tetrahedron Lett.*, 5157 (1968); W. E. McEwen, P. E. Stott, and C. M. Zepp, *J. Amer. Chem. Soc.* **95**, 8452 (1973).

⁵⁴ S. Sato, T. Mase, and M. Ohta, *Bull. Chem. Soc. Jap.* **41**, 2218 (1968).

⁵⁵ P. Roesler and J.-P. Fleury, *Bull. Soc. Chim. Fr.*, 631 (1968).

⁵⁶ M. Götz and K. Zeile, *Tetrahedron* **26**, 3185 (1970).

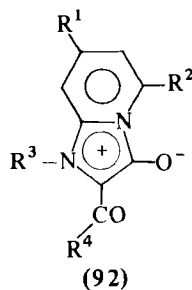
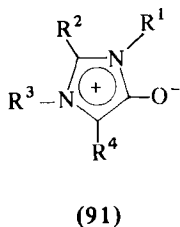
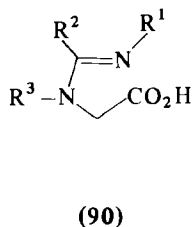
3. *1,3-Oxazol-4-imines (Anhydro-4-amino-1,3-oxazolium Hydroxides)*
(87)



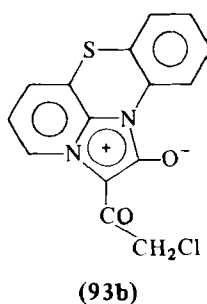
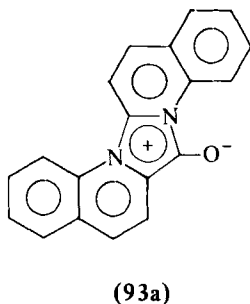
Meso-ionic 1,3-oxazol-4-imines (87) have not been isolated by basic treatment of the corresponding salts (88). These salts (88) are formed by acid-catalyzed cyclization of the nitriles (89).⁵⁷

B. DIAZOLES

1. *1,3-Diazol-4-ones (Anhydro-4-hydroxy-1,3-diazolium Hydroxides)*
(91)



Anhydro-acylation of *N*-(*N*-phenylbenzimidoyl)amino acids (90) and the corresponding nitriles yield the meso-ionic 5-acyl-1,3-diazol-4-ones (91, R⁴ = COR); derivatives (92) are analogously formed from *N*-2-pyridylglycines.^{28,58a} The meso-ionic compounds 91 and 92 are remarkably stable; they are unreactive toward alkalis, acids, and amines.



⁵⁷ A. Chinone, S. Sato, T. Mase, and M. Ohta, *Bull. Chem. Soc. Jap.* **42**, 2310 (1969).

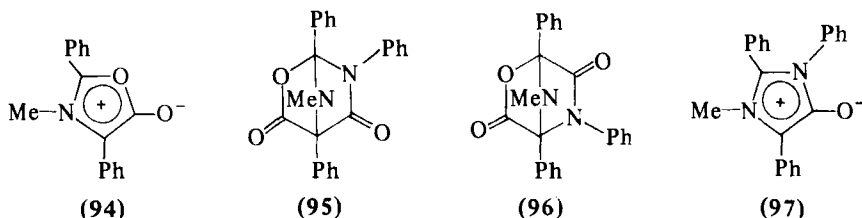
⁵⁸ (a) E. B. Roche and D. W. Stansloski, *J. Heterocyc. Chem.* **7**, 139 (1970); (b) J. W. Steele, W. K. Anderson, and W. F. Trager, *Can. J. Chem.* **50**, 1026 (1972).

Polycyclic meso-ionic 1,3-diazol-4-ones (**93**) are also known. These include Besthorn's Red (**93a**) which was first described in 1904. The discovery of Besthorn's Red and its subsequent formulation (**93a**) forms an interesting part of the history of meso-ionic compounds.^{2,9b}

Recently,^{58b} an analogous meso-ionic 1,3-diazol-4-one (**93b**) was unexpectedly encountered as the product of the reaction between 1-azaphenothiazine and chloroacetic anhydride.

The triphenyl derivative (**91**, $R^1 = R^3 = R^4 = \text{Ph}$, $R^2 = \text{H}$) is formed^{59c} in a mechanistically interesting reaction between benzoyl formic acid anil ($\text{Ph}-\text{N}=\text{CPh}-\text{CO}_2\text{H}$), trifluoroacetic anhydride, and pyridine. Its 1,3-dipolar cycloaddition reactions with alkynes and alkenes have been reported.^{59c}

Two synthetic routes⁵⁹ to meso-ionic 1,3-diazol-4-ones (**91**) have recently been reported. 1,3-Cycloaddition^{59a} of phenyl isocyanate to the meso-ionic 1,3-oxazol-5-one (**94**) yields the intermediate (**95** or **96**) from which carbon dioxide was extruded in boiling xylene, giving the meso-ionic 1,3-diazol-4-one (**97**).



A general route^{59b} to meso-ionic 1,3-diazol-4-ones (**91**) involves the reaction of amino amides ($R^1\text{NHCOCH}_2\text{NHR}^3$) either with triethyl orthoformate or with *N*-phenylbenzimidoyl chloride.

2. 1,3-Diazol-4-imines (Anhydro-4-amino-1,3-diazolium Hydroxides) (**98**)

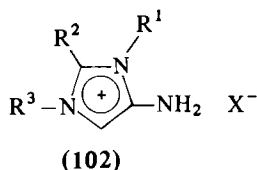
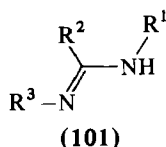
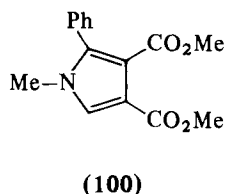
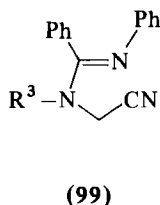
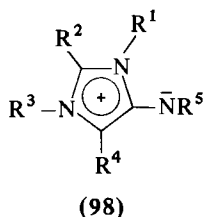
The meso-ionic 1,3-diazol-4-imine (**98**, $R^1 = R^2 = \text{Ph}$, $R^3 = \text{Me}$, $R^4 = \text{H}$, $R^5 = \text{COPh}$) has been prepared⁶⁰ from the nitrile (**99**, $R^3 = \text{Me}$) and benzoyl chloride followed by treatment with sodium hydrogen carbonate. This compound (**98**, $R^1 = R^2 = \text{Ph}$, $R^3 = \text{Me}$, $R^4 = \text{H}$, $R^5 = \text{COPh}$) undergoes a 1,3-dipolar cycloaddition with dimethyl acetylenedicarboxylate in boiling benzene during 10 minutes, yielding the pyrrole

⁵⁹ (a) T. Shiba and H. Kato, *Bull. Chem. Soc. Jap.* **43**, 3941 (1970); (b) R. Grashey, E. Jänchen, and J. Litzke, *Chem. Ztg.* **97**, 657 (1973); (c) G. Singh and P. S. Pande, *Tetrahedron Lett.*, 2169 (1974).

⁶⁰ K. T. Potts, S. Husain, and S. Husain, *Chem. Commun.*, 1360 (1970); K. T. Potts and S. Husain, *J. Org. Chem.* **36**, 3368 (1971).

(100).⁶⁰ A similar 1,3-dipolar cycloaddition occurs with diethyl azodicarboxylate, and the intermediate 1,3-cycloadduct was isolated.⁶⁰

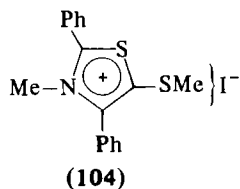
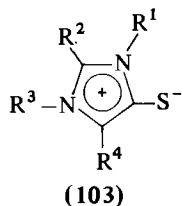
Amidines (101) and halogenoacetonitriles (XCH_2CN) yield 4-amino-1,3-diazolium salts (102) directly.⁶¹ These salts (102) could not be transformed into the corresponding meso-ionic heterocycles (98) with base;



they were unchanged by treatment with triethylamine or sodium hydrogen carbonate. Sodium hydroxide transformed the salt (102, $\text{R}^1 = \text{R}^2 = \text{R}^3 = \text{Ph}$, $\text{X} = \text{Br}$) into the amidinonitrile (99, $\text{R}^3 = \text{Ph}$). The salts (102) and acetic anhydride gave *N*-acetyl derivatives.

3. 1,3-Diazole-4-thiones (Anhydro-4-mercapto-1,3-diazolium Hydroxides) (103)

Meso-ionic 1,3-diazole-4-thiones (103, $\text{R}^1 = \text{Ph}$) have been prepared by 1,3-dipolar cycloaddition of phenylisothiocyanate to meso-ionic 1,3-oxazol-5-ones (66)⁶² and 1,3-thiazol-5-ones (105).⁶³ Another route to 1,3-diazole-4-thiones is exemplified by the formation of the derivative (103, $\text{R}^1 = \text{R}^3 = \text{Me}$, $\text{R}^2 = \text{R}^4 = \text{Ph}$) from the methiodide (104) and methylamine.⁵⁹



⁶¹ A. Chinone, S. Sato, and M. Ohta, *Bull. Chem. Soc. Jap.* **44**, 826 (1971).

⁶² R. Huisgen, E. Funke, F. C. Schaefer, H. Gotthardt, and E. Brunn, *Tetrahedron Lett.*, 1809 (1967).

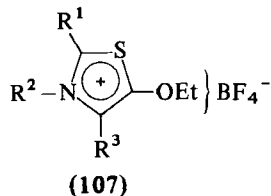
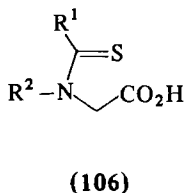
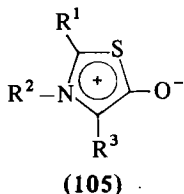
⁶³ K. T. Potts and D. N. Roy, *Chem. Commun.*, 1062 (1968).

C. THIAZOLES

1. *1,3-Thiazol-5-ones (Anhydro-5-hydroxy-1,3-thiazolium Hydroxides)* (105)

N-Alkyl- and *N*-aryl-*N*-thiobenzoylglycines (106) and hot acid anhydrides or acid chlorides in pyridine yield^{28,64} meso-ionic 4-acyl-1,3-thiazol-5-ones (105, $R^3 = R-CO$), but at room temperature 4-acylation is avoided.⁶⁵

A second route to meso-ionic 1,3-thiazol-5-ones (105) is provided by 1,3-dipolar cycloaddition. Thus, the meso-ionic 1,3-oxazol-5-one (66, $R^1 = R^3 = Ph$, $R^2 = Me$), and carbon oxysulfide yields the corresponding 1,3-thiazol-5-one (105, $R^1 = R^3 = Ph$, $R^2 = Me$).^{44,62}



The meso-ionic 1,3-thiazol-5-ones (105) show an interesting range of reactions. Electrophilic substitution reactions⁶⁵ have yielded the 4-substituted derivatives (105, $R^3 = Br, I, HgCl, HgOAc$), and triethyloxonium tetrafluoroborate gives the corresponding thiazolium salts (107).⁶⁶ Meso-ionic 1,3-thiazol-5-ones (105, $R^3 = H$ or Ph) undergo 1,3-dipolar cycloaddition with cyclopropene derivatives,^{46b,46c} diethyl azodicarboxylate,⁶² or dimethyl acetylenedicarboxylate,^{67a} but the presence of a 4-acyl substituent (105, $R^3 = COR$) prevents the cycloaddition reaction.^{67a} Good yields of adducts are also obtained if the meso-ionic 1,3-thiazol-5-ones are generated in the presence of the 1,3-dipolarophile.⁴⁶

2. *1,3-Thiazol-5-imines (Anhydro-5-amino-1,3-thiazolium Hydroxides)* (108)

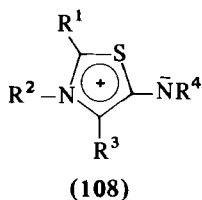
The claim⁶² that the compound 103, $R^1 = R^2 = R^4 = Ph$, $R^3 = Me$, is rearranged by hydrogen chloride in chloroform, yielding the isomer 108, $R^1 = R^3 = R^4 = Ph$, $R^2 = Me$, has not been confirmed.^{59,67b}

⁶⁴ A. Lawson and C. E. Searle, *J. Chem. Soc.*, 1556 (1957).

⁶⁵ M. Ohta, H. Chosho, C.-G. Shin, and K. Ichimura, *Nippon Kagaku Zasshi* **85**, 440 (1964) [*CA* **61**, 14657h (1964)]; M. Ohta and C. Shin, *Bull. Chem. Soc. Jap.* **38**, 704 (1965).

⁶⁶ K. T. Potts, E. Houghton, and S. Husain, *Chem. Commun.*, 1025 (1970).

⁶⁷ (a) K. T. Potts and D. N. Roy, *Chem. Commun.*, 1061 (1968); (b) T. Shiba and H. Kato, *Bull. Chem. Soc. Jap.* **44**, 1864 (1971); (c) **46**, 964 (1973).

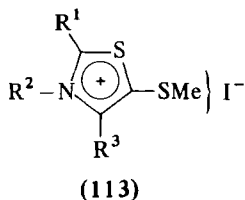
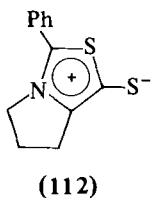
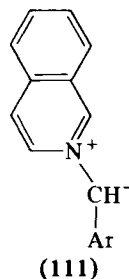
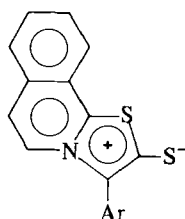
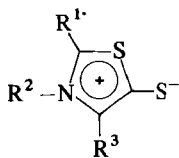


A general synthetic route to meso-ionic *N*-acyl-1,3-thiazol-5-imines (**108**, $R^1 = \text{Ph}$, $R^2 = \text{Me}$, $R^3 = \text{Me}$ or Ph , $R^4 = \text{COPh}$) is provided by treatment of thiobenzamidoaminoacetonitriles, Ph-CS-NMe-CHR-CN , first with benzoyl chloride and then with aqueous alkali. Alternatively, the thiobenzamidoaminoacetonitriles and hydrogen chloride give the corresponding salts, which with benzoyl chloride and aqueous alkali give *N*-acyl-1,3-thiazol-5-imines (**108**).^{59b, 67b}

Derivatives (**108**, $R^1 = \text{SMe}$) have been obtained by treating 5-acylamino-4-thiazoline-2-thiones with methyl iodide and aqueous alkali.^{67c}

3. 1,3-Thiazole-5-thiones (Anhydro-5-mercapto-1,3-thiazolium Hydroxides) (**109**)

Monocyclic 1,3-thiazole-5-thiones (**109**) are easily prepared by 1,3-dipolar cycloaddition of carbon disulfide to meso-ionic 1,3-oxazol-5-ones (**66**)^{44, 62} and 1,3-thiazol-5-ones (**105**).⁶⁸ Polycyclic meso-ionic 1,3-thiazole-5-thiones (**110**)⁶⁹⁻⁷¹ are formed from carbon disulfide and azomethine ylides (**111**) derived from isoquinolinium iodides and base.



⁶⁸ G. C. Barrett, A. R. Khokhar, and J. R. Chapman, *Chem. Commun.*, 818 (1969).

⁶⁹ F. Kröhnke and H. H. Steuernagel, *Angew. Chem.* **73**, 26 (1961).

⁷⁰ F. Kröhnke and H. H. Steuernagel, *Chem. Ber.* **97**, 1118 (1964).

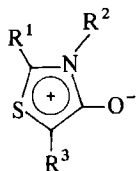
⁷¹ R. Huisgen, R. Grashey, and E. Steingruber, *Tetrahedron Lett.*, 1441 (1963).

The meso-ionic 1,3-thiazole-5-thione (112)⁶⁸ is formed from *N*-thiobenzoylproline and warm thiolactic acid.

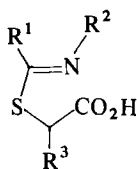
The constitution (110, Ar = *p*-Br . C₆H₄) was firmly established by X-ray crystallography.^{72a} The corresponding derivative (110, Ar = *p*-O₂N . C₆H₄) yields a methiodide which gives meso-ionic 1,3-diazole-4-thiones (103) with primary aliphatic amines.^{72b} The meso-ionic 1,3-thiazole-5-thiones (109) give the salts (113) with methyl iodide.⁵⁹

4. 1,3-Thiazol-4-ones (Anhydro-4-hydroxy-1,3-thiazolium Hydroxides) (114)

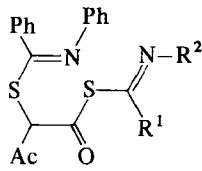
The product obtained by reaction between the acid (115, R¹ = R² = Ph, R³ = H) and acetic anhydride-triethylamine was initially thought⁷³ to be anhydro-2,3-diphenyl-4-hydroxy-1,3-thiazolium hydroxide, C₁₅H₁₁NOS (114, R¹ = R² = Ph, R³ = H), but later studies⁷⁴ established that the product had the molecular formula C₃₀H₂₄N₂O₂ and the constitution 116. The synthesis of the meso-ionic 1,3-thiazol-4-one (114, R¹ = R² = Ph, R³ = H), orange-yellow needles, m.p. 113°–115°, was successfully achieved⁷⁴ by dehydration of the acid (115, R¹ = R² = Ph, R³ = H) using acetic anhydride-triethylamine for a few minutes at room temperature. The acids (115, R¹ = NR₂, R² = Ph, R³ = H) and acid anhydrides similarly yield the corresponding meso-ionic 1,3-thiazol-4-ones (114, R¹ = NR₂, R² = Ph, R³ = H).^{75a} Analogous polycyclic meso-ionic 1,3-thiazol-4-ones have also been prepared.⁷⁵



(114)



(115)



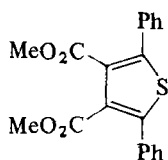
(116)

⁷² (a) J. E. Baldwin, M. C. McDaniel, M. G. Newton, and I. C. Paul, *Tetrahedron Lett.*, 4239 (1966); (b) P. B. Talukdar, S. K. Sengupta, and A. K. Datta, *J. Chem. Soc., Chem. Commun.*, 696 (1972); *Indian J. Chem.* 11, 1257 (1973); [CA 80, 133344p (1974)].

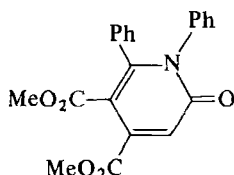
⁷³ M. Ohta, H. Chosho, C.-G. Shin, and K. Ichimura, *Nippon Kagaku Zasshi*, 85, 440 (1964); [CA 61, 14657h (1964)].

⁷⁴ K. T. Potts, U. P. Singh, and E. Houghton, *Chem. Commun.*, 1128 (1969).

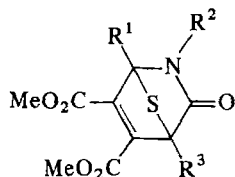
⁷⁵ (a) M. Ohta and S. Sato, *J. Chem. Soc. Jap.* 89, 199 (1968); (b) G. F. Duffin and J. D. Kendall, *J. Chem. Soc.*, 361 (1956); E. B. Knott, *ibid.*, 916, 937 (1955); (c) M. Hashimoto and M. Ohta, *Bull. Chem. Soc. Jap.* 33, 1394 (1960) [CA 55, 15470c (1961)]; (d) P. M. Kochergin, *Zh. Obshch. Khim.* 31, 3257 (1961) [CA 57, 2208c (1962)]; M. Ohta and K. Kishimoto, *Bull. Chem. Soc. Jap.* 34, 1402 (1961); (f) W. G. Salmond, *Quart. Rev., Chem. Soc.* 22, 272 (1968).



(117)



(118)



(119)

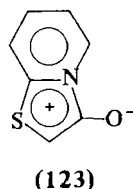
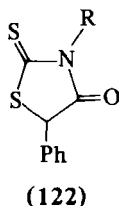
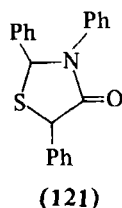
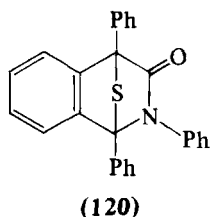
The meso-ionic 1,3-thiazol-4-ones (114) undergo a so-called 1,4-cycloaddition reaction⁷⁶ which contrasts with the 1,3-cycloadditions most frequently exhibited by meso-ionic heterocycles.³ The course of the reaction is also determined by the nature of the 5-substituent (114, $R^3 = \text{Ph}$ or H). Thus, dimethyl acetylenedicarboxylate and the triphenyl derivative (114, $R^1 = R^2 = R^3 = \text{Ph}$) yields the thiophene (117), whereas the diphenyl derivative (114, $R^1 = R^2 = \text{Ph}$, $R^3 = \text{H}$) gives the pyridone (118). The triphenyl derivative (114, $R^1 = R^2 = R^3 = \text{Ph}$) and dibenzoylacetylene in refluxing benzene by a 1,3-cycloaddition yields 3,4-dibenzoyl-2,5-diphenylthiophene, which is a useful intermediate for the synthesis of 1,3,4,6-tetraphenylthieno[3,4-*c*]thiophene.⁷⁶ These reactions have been discussed in terms of an intermediate (119) formed by a 1,3-cycloaddition which yields the thiophene (117) by elimination of phenylisocyanate, whereas the pyridone (118) is formed by sulfur extrusion. The triphenyl derivative (114, $R^1 = R^2 = R^3 = \text{Ph}$) undergoes a similar cycloaddition reaction with benzyne, yielding the intermediate adduct 120.^{77a} Thermal transformation of the adduct (120) occurred in boiling xylene giving diphenylbenzo[*c*]thiophene by elimination of phenyl isocyanate. In striking contrast, photochemical irradiation of the adduct gave 1,2,4-triphenyl-3-isoquinolone by sulfur extrusion. The final sentence of this communication^{77a} is worthy of quotation: "Such complete selectivity in thermal and photochemical fragmentation of a compound bearing two potentially extrudable groups, *though not without precedent, is unique.*"

The diphenyl derivative (114, $R^1 = R^2 = \text{Ph}$, $R^3 = \text{H}$)⁷⁴ is extremely sensitive to moisture and is decomposed by atmospheric exposure. With hot acetic anhydride this compound (114, $R^1 = R^2 = \text{Ph}$) undergoes 5-acylation (114, $R^3 = \text{H} \rightarrow R^3 = \text{Ac}$). Reduction of the triphenyl derivative (114, $R^1 = R^2 = R^3 = \text{Ph}$) with sodium borohydride yields 2,3,5-triphenylthiazolidin-4-one (121).^{77b} This compound (114, $R^1 = R^2$

⁷⁶ K. T. Potts, E. Houghton, and U. P. Singh, *Chem. Commun.*, 1129 (1969); K. T. Potts and D. McKeough, *J. Amer. Chem. Soc.* **95**, 2750 (1973).

⁷⁷ (a) S. Nakazawa, T. Kiyosawa, K. Hirakawa, and H. Kato, *J. Chem. Soc., Chem. Commun.*, 621 (1974); (b) Z. Takayanagi, H. Kato, and M. Ohta, *Bull. Chem. Soc. Jap.* **40**, 2930 (1967).

= $R^3 = \text{Ph}$) forms the corresponding thiazolium salts by treatment with acetyl or benzoyl perchlorate.^{77b}



Alkylation of 5-phenylrhodanines (122) with alkyl iodides and sodium ethoxide yields the meso-ionic 2-alkylthio-1,3-thiazol-4-ones (114, $R^1 = \text{SR}$).^{78a} The structure of the compound 114, $R^1 = \text{SMe}$, $R^2 = \text{NH}_2$, $R^3 = \text{Ph}$, was established by X-ray analysis.^{78a} The dipole moment of the compound 114, $R^1 = R^2 = \text{Me}$, $R^3 = \text{Ph}$, in benzene solution is 5.21 D.^{78a} Irradiation of the meso-ionic 1,3-thiazole-4-thione (114, $R^1 = \text{SMe}$, $R^2 = \text{Me}$, $R^3 = \text{Ph}$) in ethanol yields the isomeric 3-methyl-4-methylthio-5-phenyl-1,3-thiazol-2-one. A novel mechanism for this photochemical rearrangement has been proposed.^{78b}

The bicyclic compound 123 is well known.^{75b,79-81} It was first prepared by cyclodehydration of (2-pyridylthio)acetic acid. It is noteworthy that 123 is formed directly from *S*-acetyl-2-mercaptopyridine and chloroacetic acid.^{82,83}

5. 1,3-Thiazol-4-imines (Anhydro-4-amino-1,3-thiazolium Hydroxides) (124)

Acid-catalyzed cyclization of the nitriles 125 yields the salts 126, $R^3 = \text{H}$, but treatment of the salts 126, $R^3 = \text{H}$, with base results in decom-

⁷⁸ (a) S. Abrahamsson, A. Westerdahl, G. Isaksson, and J. Sandström, *Acta Chem. Scand.* 21, 442 (1967); (b) O. Buchardt, J. Domanus, N. Harrit, A. Holm, G. Isaksson, and J. Sandström, *J. Chem. Soc., Chem. Commun.*, 376 (1974).

⁷⁹ E. Koenigs and H. Geisler, *Ber.* 57, 2076 (1924).

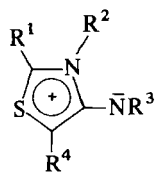
⁸⁰ A. E. Tschitschibabin and N. N. Woroshtzow, *Ber.* 66 364 (1933).

⁸¹ G. F. Duffin and J. D. Kendall, *J. Chem. Soc.*, 734 (1951).

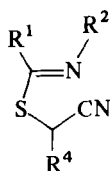
⁸² H. Kato, K. Tanaka, and M. Ohta, *Bull. Chem. Soc. Jap.* 35, 1901 (1962).

⁸³ H. Kato, K. Tanaka, and M. Ohta, *Bull. Chem. Soc. Jap.* 39, 1248 (1966).

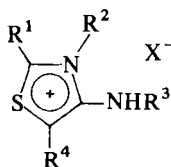
position and does not lead to the meso-ionic 1,3-thiazol-4-imines (**124**, $R^3 = H$).⁸⁴⁻⁸⁶ However, *N*-acetyl derivatives (**126**, $R^3 = Ac$) are formed by acetylation of the salts **126**, $R^3 = H$, and then treatment with base does yield *N*-acetyl derivatives of the meso-ionic 1,3-thiazol-4-imines (**124**, $R^3 = Ac$).⁸⁶ The salts **126**, $R^3 = H$ and potassium cyanate yield the *N*-carbamoyl derivatives **124**, $R^3 = CONH_2$.⁸⁶ Acid hydrolysis of the salts **126**, $R^3 = H$ or Ac , $X = Cl$, gives hydrochlorides of the amides **127**.⁸⁶



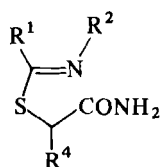
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(125)

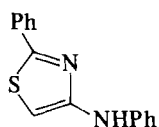


(126)

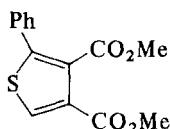


(127)

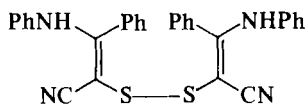
The *N*-acetyl derivatives of the 2-alkylthio-1,3-thiadiazol-4-imines (**124**, $R^1 = SR$, $R^3 = Ac$) undergo nucleophilic displacement reaction with amines (benzylamine, cyclohexylamine, morpholine, or aniline) giving the 2-amino derivatives (**124**, $R^1 = NR_2$, $R^3 = Ac$).⁸⁶ The salt (**126**, $R^1 = R^2 = Ph$, $R^3 = R^4 = H$, $X = Cl$) reacts with aniline at room temperature giving 4-anilino-2-phenyl-1,3-thiazole (**128**), presumably by a mechanism involving cleavage of the heterocyclic ring.⁸⁷



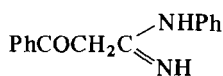
(128)



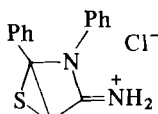
(129)



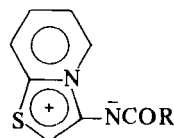
(130)



(131)



(132)



(133)

Most of the known 1,3-dipolar cycloaddition reactions of meso-ionic heterocycles³ have been concerned with those types in which the exo-

⁸⁴ M. Ohta, K. Yoshida, and S. Sato, *Bull. Chem. Soc. Japan*, **39**, 1269 (1966).

⁸⁵ H. Chosho, K. Ichimura, and M. Ohta, *Bull. Chem. Soc. Jap.*, **37**, 1670 (1964).

⁸⁶ K. Ichimura and M. Ohta, *Bull. Chem. Soc. Jap.*, **38**, 707 (1965).

⁸⁷ S. Sato and M. Ohta, *Bull. Chem. Soc. Jap.*, **41**, 2801 (1968).

cyclic substituent is either an oxygen or a sulfur atom (19, f = O or S). In these cases the formation of the heterocyclic product involves extrusion of carbon dioxide or carbonyl sulfide from the intermediate cycloadduct. An interesting extension of this reaction type is provided⁶⁰ by the formation of the thiophene 129 from anhydro-4-*N*-benzoylamino-2,3-diphenyl-1,3-thiazolium hydroxide (124, R¹ = R² = Ph, R³ = CPh, R⁴ = H) and dimethyl acetylenedicarboxylate. In this case the exocyclic substituent (19, f) is NCOPh and the transformation involves the elimination of *N*-benzoyl-*N'*-phenylcarbodiimide, Ph-CON=C=NPh, from the intermediate cycloadduct.

Interest in the photochemistry of meso-ionic compounds is now developing, and an interesting result⁸⁸ has been obtained by the photolysis of 5-amino-1,3-thiazolium salts (126, R³ = H). For example, irradiation of the salt 126, R¹ = R² = Ph, R³ = H, X = Cl, in aqueous solution yields the disulfide 130 (23%) and the keto amidine 131 (70%). It is proposed that this reaction involves a bicyclic intermediate (132).⁸⁸

Bicyclic derivatives (133) of 1,3-thiazol-4-imines have been prepared^{82,89} by treatment of (2-pyridylthio)acetonitrile with acid chlorides. The same compounds (133) are also formed from *S*-acyl-2-mercaptopyridine, chloroacetonitrile, and acid chlorides.

D. DITHIOLES

1. 1,3-Dithiol-4-ones (Anhydro-4-hydroxy-1,3-dithiolium Hydroxides) (134)

The dehydration of thiobenzoylthioglycolic acid (135, R¹ = Ph, R² = H) with acetic anhydride-boron trifluoride was initially described⁹⁰ as yielding the meso-ionic 1,3-dithiol-4-one (134, R¹ = Ph, R² = H), but subsequent studies⁹¹ showed that the product was in fact the 5-substituted derivative 134, R¹ = Ph, R² = COCH₂SCSPh. Authentic meso-ionic 1,3-dithiol-4-ones (134) have recently been prepared^{91,92} (85–90% yield) by the cyclodehydration of the acids (135) with acetic anhydride-triethylamine at 0°–10°. Examples include anhydro-4-hydroxy-2-phenyl-1,3-dithiolium hydroxide (134, R¹ = Ph, R² = H)⁹¹ described as scarlet needles, m.p. 113°–115°; this compound is sensitive to moisture. Anhydro-4-hydroxy-2,5-diphenyl-1,3-dithiolium hydroxide (134, R¹ = R² = Ph)⁹² was obtained as gold lustered, deep violet needles,

⁸⁸ A. Chinone, Y. Huseya, and M. Ohta, *Bull. Chem. Soc. Jap.* **43**, 2650 (1970).

⁸⁹ H. Kato and M. Ohta, *Bull. Chem. Soc. Jap.* **39**, 1253 (1966).

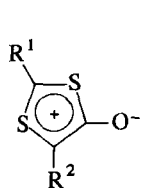
⁹⁰ M. Ohta and M. Sugiyama, *Bull. Chem. Soc. Jap.* **38**, 596 (1965).

⁹¹ K. T. Potts and U. P. Singh, *Chem. Commun.*, 569 (1969).

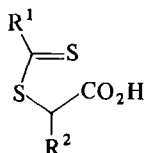
⁹² H. Gotthardt and B. Christl, *Tetrahedron Lett.*, 4743 (1968).

m.p. 150°–151°; its dipole moment (4.96 D, benzene) is in accord with its meso-ionic formulation.

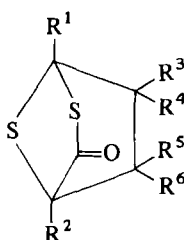
The meso-ionic 1,3-dithiol-4-ones (134) participate^{46a,77a,91,93,94} in 1,3-dipolar cycloaddition reactions giving adducts of the general type 136. They show a remarkable degree of reactivity toward simple alkenes⁹⁴ including tetramethylethylene, cyclopentene, norbornene, and norbornadiene as well as toward the more reactive 1,3-dipolarophilic olefins: dimethyl maleate, dimethyl fumarate, methyl cinnamate, dibenzoylene, *N*-phenylmaleimide, and acenaphthylene. Alkynes^{91,93} such as dimethyl acetylenedicarboxylate also add to meso-ionic 1,3-dithiol-4-ones (134), but the intermediate cycloadducts are not isolable: they eliminate carbonyl sulfide and yield thiophenes (137) directly.^{91,93}



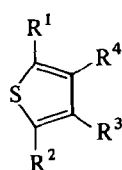
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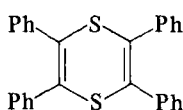
(135)



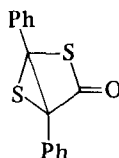
(136)



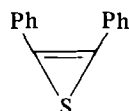
(137)



(138)



(139)



(140)

Photolysis of anhydro-4-hydroxy-2,5-diphenyl-1,3-dithiolium hydroxide (134, $R^1 = R^2 = \text{Ph}$) in benzene solution yields tetraphenyl-1,4-dithiin (138, 19% yield), diphenylacetylene (16% yield), and sulfur. This result has been interpreted⁹³ as involving the bicyclic photointermediate 139, which loses carbonyl sulfide to give the 4π -antiaromatic diphenyl thiiren (140), which is the precursor of diphenylacetylene and tetraphenyl-1,4-dithiin (138).

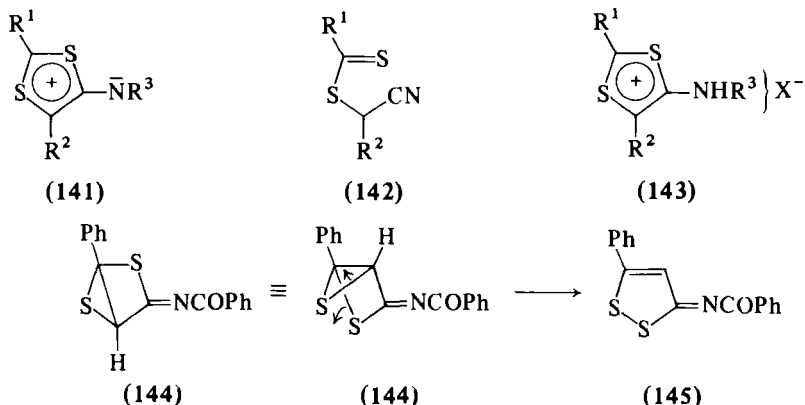
⁹³ H. Gotthardt and B. Christl, *Tetrahedron Lett.*, 4747 (1968).

⁹⁴ H. Gotthardt and B. Christl, *Tetrahedron Lett.*, 4751 (1968).

⁹⁵ H. Kato, M. Kawamura, T. Shiba and M. Ohta, *Chem. Commun.*, 959 (1970).

2. 1,3-Dithiol-4-imines (Anhydro-4-amino-1,3-dithiolium Hydroxides) (141)

The cyanomethyl dithio ester (142, $R^1 = \text{Ph}$, $R^2 = \text{H}$) and an ethereal solution of hydrogen chloride yields the salt 143, $R^1 = \text{Ph}$, $R^2 = R^3 = \text{H}$, $X = \text{Cl}$.⁹⁶ This hydrochloride (143, $R^1 = \text{Ph}$, $R^2 = \text{H}$) could not be acylated directly, but the cyanomethyl dithio ester (142, $R^1 = \text{Ph}$, $R^2 = \text{H}$) with benzoyl or acetyl chloride gave the salts 143, $R^1 = \text{Ph}$, $R^2 = \text{H}$, $R^3 = \text{COPh}$ or COMe , which with aqueous sodium hydrogen carbonate gave the red meso-ionic derivatives 141, $R^1 = \text{Ph}$, $R^2 = \text{H}$, $R^3 = \text{COPh}$ or COMe .^{90,96}



Irradiation of a benzene solution of anhydro-4-benzoylamino-2-phenyl-1,3-dithiolium hydroxide (141, $R^1 = \text{Ph}$, $R^2 = \text{H}$, $R^3 = \text{COPh}$) yields the 1,2-dithiole (145, 80%). This photoisomerization has been interpreted as involving the bicyclic intermediate 144.⁹⁷

E. OXADIAZOLES

1. 1,3,4-Oxadiazol-2-ones (Anhydro-2-hydroxy-1,3,4-oxadiazolium Hydroxides) (146)

These meso-ionic compounds are often referred to as isosydnone (146). They are prepared from *N*-acyl-*N*-(alkyl or aryl)-hydrazines (147, $X = \text{O}$) or their hydrochlorides and carbonyl chloride.⁹⁸⁻¹⁰¹ The isosyd-

⁹⁶ M. Ohta and M. Sugiyama, *Bull. Chem. Soc. Jap.* **36**, 1437 (1963).

⁹⁷ (a) H. Kato, T. Shiba, H. Yoshida, and S. Fujimori, *Chem. Commun.*, 1591 (1970);

(b) H. Kato, T. Shiba, and Y. Miki, *J. Chem. Soc., Chem. Commun.*, 498 (1972).

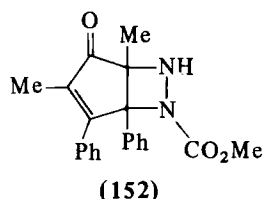
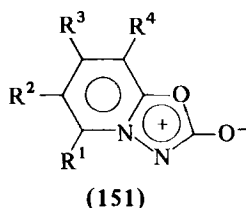
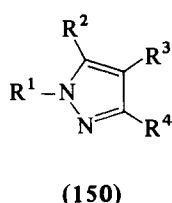
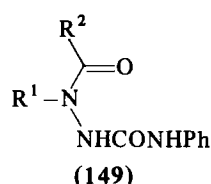
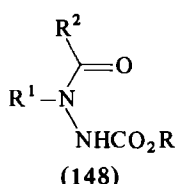
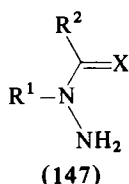
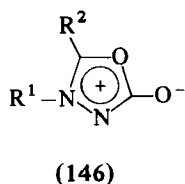
⁹⁸ M. Hashimoto and M. Ohta, *Bull. Chem. Soc. Jap.* **34**, 668 (1961).

⁹⁹ E. B. Roche and L. B. Kier, *J. Pharm. Sci.* **54**, 1700 (1965).

¹⁰⁰ C. Ainsworth, *Can. J. Chem.* **43**, 1607 (1965).

¹⁰¹ D. J. McCaustland, W. H. Burton, and C. C. Cheng, *J. Heterocycl. Chem.* **8**, 89 (1971).

nones (146) are colorless, reasonably stable compounds, but they are clearly more reactive toward nucleophilic reagents¹⁰² than the sydnones (1). On heating with the indicated reagents, the following products are formed:^{20,98,103} water gives *N*-acylhydrazines (147, X = O) and the corresponding urea derivative, alcohols give urethans (148), and aniline gives *N*-phenylureas (149). The reaction of isosydnone (146) with hydrogen sulfide in the presence of the tertiary bases, pyridine or triethylamine, provides a useful synthetic route of *N*-thioacylhydrazines (147, X = S).¹⁰³



The dipole moment of 4,5-diphenyl isosydnone (146, R¹ = R² = Ph) is 7.82 D (benzene), and comparison with the dipole moments of other diaryl isosydnone has given a value of 7.3 D for the isosydnone group moment.¹⁹ This and the spectroscopic properties of isosydnone are in full accord with their meso-ionic formulation (146).¹⁹

Isosydnone (146) react with alkynes to give pyrazoles (150). For example, 4,5-diphenylisoydnone (146, R¹ = R² = Ph) and ethyl phenyl propiolate gives 4-ethoxycarbonyl-1,3,5-triphenylpyrazole (150, R¹ = R² = R⁴ = Ph, R³ = CO₂Et) identical with the product from 4,5-diphenylsydnone (1, R¹ = R² = Ph).¹⁰⁴ The rate of 1,3-cycloaddition for isosydnone (146) is relatively slow in comparison with sydnones (1).^{20,104} A number of other cycloaddition reactions of isosydnone with alkenes, alkynes, and carbonyl compounds have been reported.²⁰

The first isosydnone to be prepared^{105a} was the bicyclic derivative

¹⁰² P. B. Talukdar, S. Banerjee, and A. Chakraborty, *Indian J. Chem.* **10**, 610 (1972).

¹⁰³ A. R. McCarthy, W. D. Ollis, and C. A. Ramsden, *Chem. Commun.* 499 (1968); *J. Chem. Soc. Perkin Trans. I*, 627 (1974).

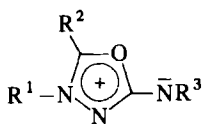
¹⁰⁴ R. Huisgen, H. Gotthardt, and R. Grashey, *Chem. Ber.* **101**, 536 (1968).

¹⁰⁵ (a) K. Hoegerle, *Helv. Chim. Acta* **41**, 548 (1958); (b) A. Balasubramanian, J. M. McIntosh, and V. Snieckus, *J. Org. Chem.* **35**, 433 (1970).

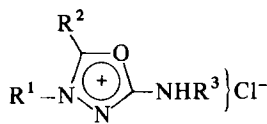
151, $R^1 = R^2 = R^3 = R^4 = H$, formed from 1-aminopyrid-2-one and carbonyl chloride. This substance (**151**, $R^1 = R^2 = R^3 = R^4 = H$) is unchanged by irradiation at 350 and 300 nm.^{105b} Recently the formation of the bicyclic derivative **151**, $R^1 = R^4 = Me$, $R^2 = R^3 = Ph$, by an unusual rearrangement has been reported.¹⁰⁶ The bicyclic diazetidine ester (**152**) and trifluoroacetic acid gave an isomeric α -pyridone, which yielded the bicyclic meso-ionic compound **151**, $R^1 = R^4 = Me$, $R^2 = R^3 = Ph$, on heating.¹⁰⁶

2. 1,3,4-Oxadiazol-2-imines (Anhydro-2-amino-1,3,4-oxadiazolium Hydroxides) (**153**)

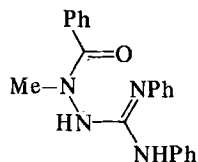
This new class of meso-ionic compounds have been recently synthesized.^{107a} *N*-Methyl-*N*-benzoylhydrazine (**147**, $R^1 = Me$, $R^2 = Ph$) and aryl isocyanide dichlorides ($ArN=CCl_2$) yield 1,3,4-oxadiazolium chlorides (**154**, $R^1 = Me$, $R^2 = Ph$, $R^3 = Ar$), which with diazomethane give the meso-ionic 1,3,4-oxadiazol-2-imines (**153**) as yellow crystalline compounds. Subsequently this synthetic method¹⁰⁷ has been extended by the use of acylisocyanide dichlorides. These reagents yield the 1,3,4-oxadiazol-2-imines **153**, $R^3 = SO_2R$,^{107b} and **153**, $R^3 = COR$.^{107c}



(153)



(154)



(155)

The derivative **153**, $R^1 = Me$, $R^2 = R^3 = Ph$, has a dipole moment ($\mu = 7.56$ D) in accord with its meso-ionic structure.¹⁰⁸ The meso-ionic 1,3,4-oxadiazol-2-imine (**153**, $R^1 = Me$, $R^2 = R^3 = Ph$) reacts with aniline giving the guanidine derivative **155**.^{107a}

3. 1,3,4-Oxadiazole-2-thiones (Anhydro-2-mercapto-1,3,4-oxadiazolium Hydroxides) (**156**)

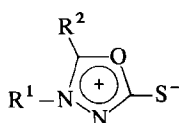
A representative of this class (**156**, $R^1 = Me$, $R^2 = Ph$) was first ob-

¹⁰⁶ D. Mackay and L. L. Wong, *J. Chem. Soc., Chem. Commun.*, 621 (1974).

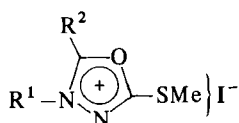
¹⁰⁷ (a) W. D. Ollis and C. A. Ramsden, *Chem. Commun.*, 1223 (1971); *J. Chem. Soc., Perkin Trans. I*, 642 (1974); (b) R. Grashey, R. Hamprecht, N. Keramaris, and M. Baumann, *Tetrahedron Lett.*, 2943 (1972); (c) A. Ya. Lazaris, S. M. Shmuilovich, and A. N. Egorochkin, *Khim. Geterotsikl. Soedin.*, 1345 (1973) [*CA* **80**, 271752 (1974)]; A. Ya. Lazaris and A. N. Egorochkin, *ibid.*, 648 (1975) [*CA* **83**, 79164b (1975)].

¹⁰⁸ R. N. Hanley, W. D. Ollis, C. A. Ramsden, G. R. Rowlands, and L. E. Sutton, *J. Chem. Soc., Perkin Trans. II*, in press (1976).

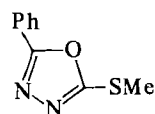
tained¹⁰⁹ by heating in pyridine the methiodide (157, $R^1 = \text{Me}$, $R^2 = \text{Ph}$) derived from 2-phenyl-4-methylthio-1,3,4-oxadiazole (158). Subsequently three general methods for the synthesis of meso-ionic 1,3,4-oxadiazole-2-thiones (156) have been described. These involve (i) the cyclization of the dithiocarbamic acid ammonium salts (159) with phosphorus oxychloride-triethylamine,^{110,111} (ii) the reaction between *N*-acylhydrazines (147) and thiophosgene,¹¹² and (iii) the condensation of *N*-acylhydrazines (147) and carbon disulfide with diethyl carbo-diimide.¹¹² The reactions of the diphenyl derivative 156, $R^1 = R^2 = \text{Ph}$, with acid, alkali, ethanol, cyclohexylamine, and triethyloxonium tetra-fluoroborate are straightforward.^{112b}



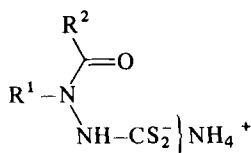
(156)



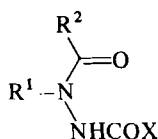
(157)



(158)

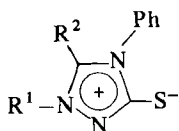


(159)

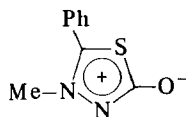


(160)

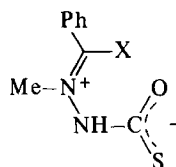
- (a) $X = \text{SMe}$
 (b) $X = \text{NHPh}$
 (c) $X = \text{NEt}_2$



(161)



(162)

(163) $X = \text{OEt}$ or SEt

The 1,3,4-oxadiazole-2-thione (156, $R^1 = \text{Me}$, $R^2 = \text{Ph}$) has a dipole moment of 9.10 D, which obviously supports its meso-ionic formulation.¹¹³ The meso-ionic 1,3,4-oxadiazole-2-thiones (156) form methiodides (157)¹¹² which are easily hydrolyzed, yielding the acyclic esters (160a). The meso-ionic 1,3,4-oxadiazole-2-thione (156, $R^1 = \text{Me}$, R^2

¹⁰⁹ J. Sandström and I. Wennerbeck, *Acta Chem. Scand.* **20**, 57 (1966).

¹¹⁰ A. Ya. Lazaris, *J. Org. Chem. USSR* **3**, 1856 (1967) [*CA* **68**, 12910p (1968)].

¹¹¹ A. Ya. Lazaris, *J. Org. Chem. USSR* **4**, 1786 (1968) [*CA* **70**, 19992s (1969)].

¹¹² (a) R. Grashey, N. Keramaris, and M. Baumann, *Tetrahedron Lett.*, 5087 (1970);
 (b) A. Ya. Lazaris and A. N. Egorochkin, *J. Org. Chem. USSR* **8**, 1569 (1972) [*CA* **77**, 139907j (1972)].

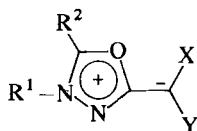
¹¹³ C. W. Atkin, A. N. M. Barnes, P. G. Edgerley, and L. E. Sutton, *J. Chem. Soc. B*, 1194 (1969).

= Ph) is transformed by reaction with aniline into the 1,2,4-triazole-3-thione (**161**, $R^1 = \text{Me}$, $R^2 = \text{Ph}$);¹⁰³ the presumption that this transformation involves the thiosemicarbazide **160b** as an intermediate is supported by the isolation of the derivative **160c** by a similar reaction with diethylamine.¹⁰³

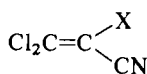
The existence of the isomeric meso-ionic compounds **156** and **162** has been recently established.^{102,103} The transformation **156** \rightarrow **162**, $R^1 = \text{Me}$, $R^2 = \text{Ph}$, is achieved by heating in ethanolic solution or with ethane-thiol in benzene; this isomerization could well involve the betaine intermediate (**163**).^{102,103}

4. 1,3,4-Oxadiazol-2-enes (Anhydro-2-alkyl-1,3,4-oxadiazolium Hydroxides) (**164**)

Representatives of this novel class of meso-ionic compounds in which the exocyclic substituent f (see Table I) is a stabilized carbanionoid residue [$-\bar{\text{C}}(\text{CN})\text{CO}_2\text{Me}$ or $-\bar{\text{C}}(\text{CN})_2$] have been recently synthesized. Base-catalyzed (potassium carbonate or triethylamine) condensation of *N*-acylhydrazines (**147**) with 3,3-dichloroacrylonitriles (**165**) yield the greenish-yellow meso-ionic 1,3,4-oxadiazol-2-enes (**164**) directly.¹¹⁴

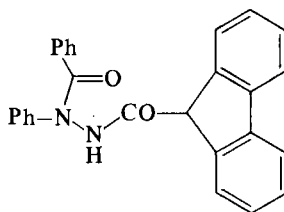


(164)

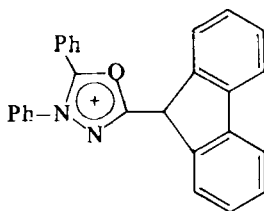


(165)

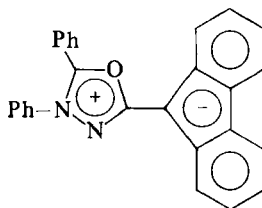
X and Y = CN or CO₂Me



(166)



(167)



(168)

An analogous meso-ionic 1,3,4-oxadiazol-2-ene (**168**) in which the negative charge is associated with a fluorenyl residue has also been recently described.¹¹⁵ The *N,N'*-diacylhydrazine (**166**) and acetic

¹¹⁴ R. Grashey, M. Baumann, and R. Hamprecht, *Tetrahedron Lett.*, 5083 (1970).

¹¹⁵ G. V. Boyd and M. D. Harms, *J. Chem. Soc. C*, 807 (1970).

anhydride-perchloric acid yield the 1,3,4-oxadiazolium perchlorate (167), which by addition of triethylamine to its solution in acetonitrile yields the purple meso-ionic compound 168, m.p. 105°–107°.

5. 1,2,3-Oxadiazol-5-ones (Sydnones) (1)

Comprehensive reviews of the chemistry of sydnones (1) have been published elsewhere,²⁻⁹ and a general discussion of this subject is not included here. Recent work on the photochemistry (Section IX), physical and theoretical studies (Section XI), and pharmacological activity (Section XII) of sydnones (1) is included in later sections.

6. 1,2,3-Oxadiazol-5-imines (Sydnone Imines) (2)

The chemistry of sydnone imines (2) has been reviewed,²⁻⁹ and a discussion of their chemistry is not duplicated here. Recent photochemical and pharmacological studies are included in Sections IX and XII.

F. OXATHIAZOLES

1,3,2-Oxathiazol-5-ones (Anhydro-5-hydroxy-1,3,2-oxathiazolium Hydroxides) (169)

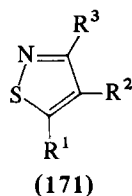
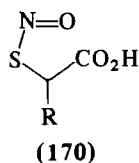
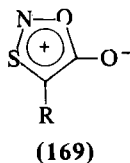
1-Mercaptophenylacetic acid, acetic anhydride, and sodium nitrite yielded the first example¹¹⁶ (169, R = Ph) of a meso-ionic 1,3,2-oxathiazol-5-one; this compound has a dipole moment of 4.5 D. An X-ray crystallographic investigation of the 4-phenyl-1,3,2-oxathiazol-5-one (169, R = Ph) has been reported.¹¹⁷ This compound is incorrectly described as a "thiosydnone." The bond distances support the structure with tetravalent sulfur, and on this evidence alone the compound 169, R = Ph, could be judged not to be "meso-ionic" because it can, on the basis of the X-ray evidence,¹¹⁷ be more satisfactorily represented by a covalent formulation.

More extensive studies¹¹⁸ have shown that α -mercaptocarboxylic acids, ethyl nitrite, and *N,N'*-dicyclohexylcarbodiimide with a catalytic amount of sulfuric acid yield meso-ionic 1,3,2-oxathiazole-5-ones (169), presumably via intermediate *S*-nitroso derivatives (170).

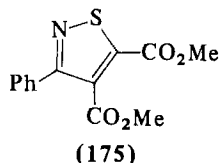
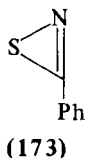
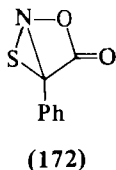
¹¹⁶ T. Bacchetti and A. Alemagna, *Atti Accad. Naz. Lincei, Rend. Cl. Sci. Fis. Mat. Nat.* **28**, 646 (1960) [*CA* **55**, 9382c (1961)].

¹¹⁷ G. D. Andreotti, G. Bocelli, L. Cavalca, and P. Sgarabotto, *Gazz. Chim. Ital.* **102**, 23 (1972) [*CA* **77**, 10803t (1972)].

¹¹⁸ (a) H. Gotthardt, *Tetrahedron Lett.*, 1277, 1281 (1971); *Chem. Ber.* **105**, 188, 196 (1972); (b) A. Alemagna and T. Bacchetti, *Chim. Ind. (Milan)* **54**, 1105 (1972) [*CA* **78**, 97561e (1973)]; (c) A. Holm, N. Harrit, K. Bechgaard, O. Buchardt, and S. E. Harnung, *J. Chem. Soc., Chem. Commun.*, 1125 (1972).



The meso-ionic 1,3,2-oxathiazol-5-ones (169) show an interesting range of reactions with nucleophiles including ammonia, primary amines, and aqueous alkali. They also react with 1,3-dipolarophiles,¹¹⁸ including dimethyl acetylenedicarboxylate and methyl propiolate, yielding isothiazoles (171) and carbon dioxide. 1,3-Dipolar cycloaddition reactions with alkenes such as styrene, dimethyl maleate, and methyl cinnamate also lead to isothiazoles (171) directly. Bicyclic intermediates (cf. 136) were not isolable; these cycloaddition reactions with alkenes giving isothiazoles involve an additional dehydrogenation step.



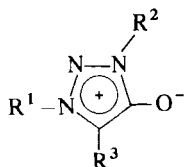
Photolysis (4045–4078 Å) of anhydro-5-hydroxy-1,3,2-oxathiazolium hydroxide (169, R = Ph) gives benzonitrile (77%), sulfur (> 90%), and carbon dioxide.¹¹⁸ This reaction has been interpreted¹¹⁸ as involving the bicyclic intermediate 172, which then transforms via the thiazirin 173 into the thiobenzonitrile oxide 174. The postulated intermediates 172 and 173 are analogous to those proposed (139 and 140) for another photoreaction.⁹⁵ The possible involvement of the thionitrile oxide 174 is indicated by its trapping with dimethyl acetylene dicarboxylate: this yields 4,5-dimethoxycarbonyl-3-phenylisothiazole (175).¹¹⁸

G. TRIAZOLES

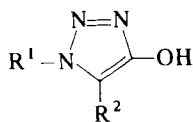
1. 1,2,3-Triazol-4-ones (*Anhydro-4-hydroxy-1,2,3-triazolium Hydroxides*) (176)

Four methods have been described for the synthesis of meso-ionic 1,2,3-triazol-4-ones (176). Alkylation of either 1-substituted 4-hydroxy-1,2,3-triazoles (177) or 5-hydroxy-1,2,3-triazoles (178) gives mixtures of

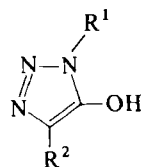
products including meso-ionic 1,2,3-triazol-4-ones (176).¹¹⁹⁻¹²⁴ This *N*-alkylation has been achieved either with diazomethane or by treating the sodium salts with alkyl halides. 1-Substituted 4- or 5-methoxy-1,2,3-triazoles are rearranged to their meso-ionic isomers in the presence of methyl iodide.^{121,122} Thus, 1-methyl-5-methoxy-1,2,3-triazole (179) and methyl iodide in chloroform give anhydro-4-hydroxy-1,3-dimethyl-1,2,3-triazolium hydroxide (180) in high yield; this reaction has been monitored by nuclear magnetic resonance (NMR) spectroscopy and has been shown to involve the cation 181 as an intermediate.^{121,122} The formation of the meso-ionic 5-bromo-1,2,3-triazol-4-one (182) from the triazolium *p*-toluenesulfonate (183a) and aqueous sodium hydroxide is interesting mechanistically and is believed to involve an ylide intermediate.^{125,126} Analogously, 1,3-dimethyl-1,2,3-triazolium tosylate (183b), *N*-bromoacetamide, and aqueous sodium hydroxide give the meso-ionic 1,2,3-triazole-4-one (182) (71% yield).¹²⁵



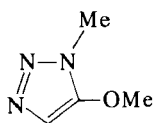
(176)



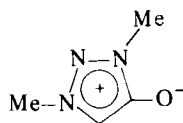
(177)



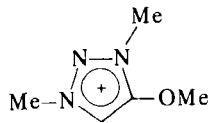
(178)



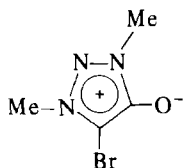
(179)



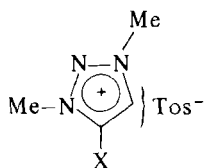
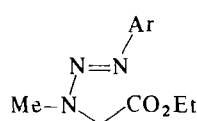
(180)



(181)



(182)

(183a) X = Br
(183b) X = H

(184)

¹¹⁹ R. Scarpatti, D. Sica, and A. Lionetti, *Gazz. Chim. Ital.* **93**, 90 (1963).

¹²⁰ M. Begtrup and C. Pedersen, *Acta Chem. Scand.* **19**, 2022 (1965).

¹²¹ M. Begtrup and C. Pedersen, *Acta Chem. Scand.* **20**, 1555 (1966).

¹²² M. Begtrup and C. Pedersen, *Acta Chem. Scand.* **21**, 633 (1967).

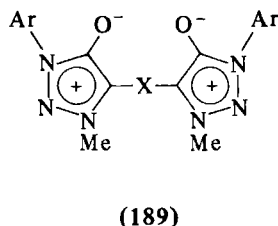
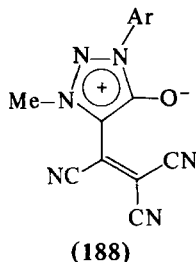
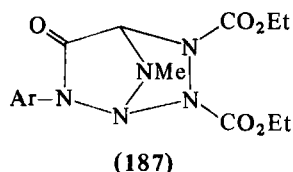
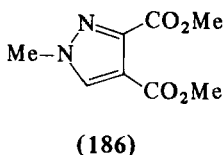
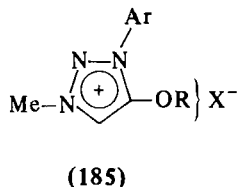
¹²³ M. Begtrup, K. Hansen, and C. Pedersen, *Acta Chem. Scand.* **21**, 1234 (1967).

¹²⁴ M. Begtrup and C. Pedersen, *Acta Chem. Scand.* **23**, 1091 (1969).

¹²⁵ M. Begtrup and P. A. Kristensen, *Acta Chem. Scand.* **23**, 2733 (1969); M. Begtrup and K. V. Poulsen, *ibid.* **25**, 2087 (1971).

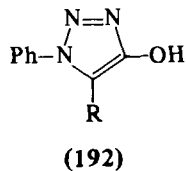
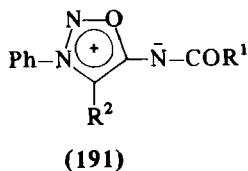
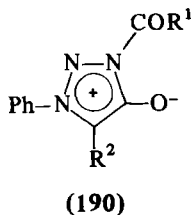
¹²⁶ M. Begtrup, *Acta Chem. Scand.* **25**, 249, 795, 803, 3500 (1971).

Cyclization of arylazoaminoacetates (184) with thionyl chloride-pyridine gives anhydro-4-hydroxy-3-aryl-1-methyl-1,2,3-triazolium hydroxides (176, $R^1 = \text{Me}$, $R^2 = \text{H}$, $R^3 = \text{Ar}$).¹²⁷ These compounds are usually basic and yield the corresponding triazolium chlorides (185, $R = \text{H}$, $X = \text{Cl}$) with hydrogen chloride in benzene solution; corresponding *O*-ethylation yielding the salts 185, $R = \text{Et}$, $X = \text{BF}_4$, takes place with triethyloxonium tetrafluoroborate.¹²⁷ They undergo 1,3-cycloaddition reactions.¹²⁷ The meso-ionic compounds 176, $R^1 = \text{Me}$, $R^2 = p\text{-Me} \cdot \text{C}_6\text{H}_4$, $R^3 = \text{H}$, and dimethyl acetylenedicarboxylate give the pyrazole 186, whereas with diethyl azodicarboxylate the 1,3-cycloadduct (187, $\text{Ar} = p\text{-Me} \cdot \text{C}_6\text{H}_4$) could be isolated.¹²⁷ In contrast, tetracyanoethylene yields the product 188, $\text{Ar} = p\text{-Me} \cdot \text{C}_6\text{H}_4$.¹²⁷ It is noteworthy that the heterocumulenes phenyl isocyanate and phenyl isothiocyanate did not react with the meso-ionic 1,2,3-triazol-4-one (176, $R^1 = \text{Me}$, $R^2 = \text{Ph}$, $R^3 = \text{H}$), but with these two heterocumulenes and the compound 176, $R^1 = R^2 = \text{Me}$, $R^3 = \text{H}$, the expected 1,3-dipolar cycloaddition was observed.¹²⁷



The 5-unsubstituted-1,2,3-triazol-4-ones (176, $R^3 = \text{H}$) participate in electrophilic substitution reactions. Bromination in chloroform of anhydro-4-hydroxy-1,3-dimethyl-1,2,3-triazolium hydroxide (180) gave its 5-bromo derivative (182).¹²¹ The meso-ionic 3-aryl-1,2,3-triazol-4-ones (176, $R^1 = \text{Me}$, $R^2 = \text{Ar}$, $R^3 = \text{H}$) gave 5-bromo derivatives (176, $R^1 = \text{Me}$, $R^2 = \text{Ar}$, $R^3 = \text{Br}$) with bromine in acetic acid. Their reaction with sulphur monochloride gave the sulfide (189, $X = \text{S}$), and with thionyl chloride they gave the sulfoxide (189, $X = \text{SO}$).¹²⁷

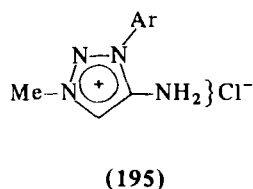
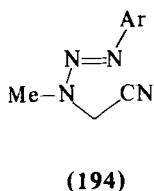
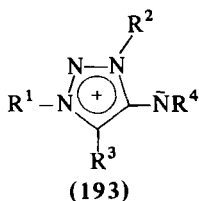
¹²⁷ K. T. Potts and S. Husain, *J. Org. Chem.* 35, 3451 (1970); 37, 2049 (1972).



Meso-ionic 3-acyl-1-phenyl-1,2,3-triazol-4-ones (**190**, $R^1 = \text{Ph}$ or Me , $R^2 = \text{H}$) have been postulated as intermediates in the interesting base-catalyzed transformation of *N*-acylsydnone imines (**191**, $R^1 = \text{Ph}$ or Me , $R^2 = \text{H}$) into 4-hydroxy-1-phenyl-1,2,3-triazole (**192**, $R = \text{H}$).^{128a} A similar photochemical transformation (**191** \rightarrow **190**, $R^1 = \text{Me}$ or Ph , $R^2 = \text{Ph}$) has also been reported.^{128b} A different base-catalyzed transformation of sydnone imine derivatives into pyrazolones has been recently reported.¹²⁹

2. 1,2,3-Triazol-4-imines (Anhydro-4-amino-1,2,3-triazolium Hydroxides) (**193**)

The *N*-methyl-*N'*-aryloaminoacetonitriles (**194**) and hydrogen chloride in ether yield the 1,2,3-triazolium chlorides (**195**). These salts (**195**) and base did not give the corresponding meso-ionic compounds (**193**, $R^1 = \text{Me}$, $R^2 = \text{Ar}$, $R^3 = R^4 = \text{H}$), but the corresponding *N*-acetyl derivatives (**193**, $R^1 = \text{Me}$, $R^2 = \text{Ar}$, $R^3 = \text{H}$, $R^4 = \text{Ac}$) were produced either from the nitriles (**194**) and acetyl chloride or from the 1,2,3-triazolium chlorides (**195**) and acetic anhydride, followed by treatment with ammonium hydroxide.¹²⁷

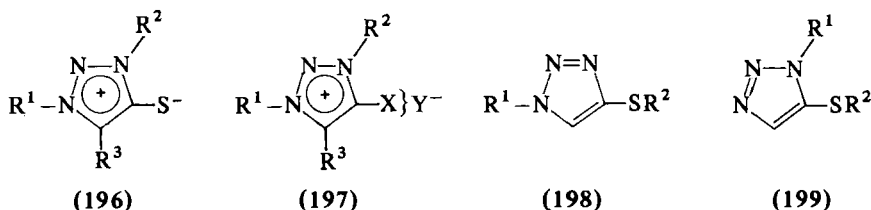


¹²⁸ (a) H. U. Daeniker and J. Druey, *Helv. Chim. Acta* **45**, 2441 (1962); H. U. Daeniker, *ibid.* **47**, 33 (1964); (b) A. Chinone and M. Ohta, *Chem. Lett.*, 969 (1972).

¹²⁹ Y. Saito, T. Teraji, and T. Kamiya, *Tetrahedron Lett.*, 2893 (1971).

3. 1,2,3-Triazole-4-thiones (Anhydro-4-mercapto-1,2,3-triazolium Hydroxides) (196)

Two general methods have been described for the synthesis of this new class of meso-ionic compounds (196).^{126,130} The most convenient method is by the treatment of 4-bromo-1,2,3-triazolium salts (197, X = Br) with sodium sulfide in dimethylformamide. Alternatively, *N*-methylation of the isomeric 4- or 5-alkylmercapto-1,2,3-triazoles 198 or 199 with methyl tosylate gave intermediate triazolium salts (197, X = SR, Y = Tos), which yielded meso-ionic 1,2,3-triazole-4-thiones (196) by *S*-dealkylation by heating with piperidine.



In contrast with the meso-ionic 1,2,3-triazol-4-ones (176) which are relatively stable to heat, the meso-ionic 1,2,3-triazole-4-thiones (196) rearrange when heated in benzene solution at 180°. Under these conditions, anhydro-1-benzyl-3-methyl-4-mercapto-1,2,3-triazolium hydroxide (196, R¹ = PhCH₂, R² = Me, R³ = H) gives a mixture of the 5-alkylmercapto-1,2,3-triazoles (199, R¹ = Me, R² = PhCH₂, 82% yield; 199, R¹ = R² = PhCH₂, 2% yield; and 199, R¹ = R² = Me, 13% yield) formed by intermolecular alkyl group transfer reactions.¹³⁰ The meso-ionic 1,2,3-triazole-4-thiones (196) and methyl iodide give methiodides (197, X = SMe, Y = I). Anhydro-1-benzyl-4-mercapto-3-methyl-1,2,3-triazolium hydroxide (196, R¹ = PhCH₂, R² = Me, R³ = H) on heating with benzoyl chloride-pyridine gives a mixture of 1,2,3-triazoles (198, R¹ = PhCH₂, R² = PhCO, 32% yield; and 199, R¹ = Me, R² = PhCO, 49% yield). This reaction presumably involves the *S*-benzoyl-1,2,3-triazolium salt (197, R¹ = PhCH₂, R² = Me, X = SCOPh, Y = Cl) as an intermediate.¹³⁰

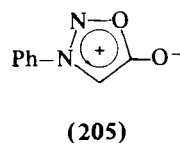
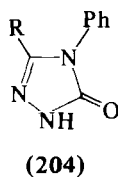
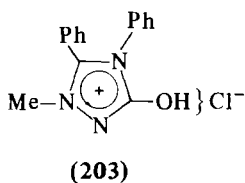
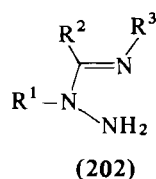
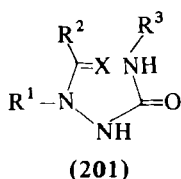
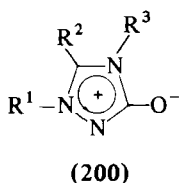
4. 1,2,4-Triazol-3-ones (Anhydro-3-hydroxy-1,2,4-triazolium Hydroxides) (200)

The "endoxytriazolines" originally described by Busch were later formulated^{2b} either as meso-ionic 1,2,4-triazol-3-ones (200) or as meso-ionic 1,3,4-oxadiazol-2-imines (153). This ambiguity has now been

¹³⁰ M. Begtrup, *Tetrahedron Lett.*, 1577 (1971); *Acta Chem. Scand.* 26, 1243 (1972).

resolved by the specific synthesis¹⁰⁷ of the meso-ionic 1,3,4-oxadiazol-2-imines (153), and recent studies^{131,132} have firmly established that Busch's "endoxytriazolines" are meso-ionic 1,2,4-triazol-3-ones (200).

A number of general methods for the synthesis of meso-ionic 1,2,4-triazol-3-ones are available. Sodium ethoxide-catalyzed cyclization of 1-benzoyl-1,4-diphenylsemicarbazide (201, $R^1 = R^2 = R^3 = \text{Ph}$, $X = \text{O}$) yielded anhydro-3-hydroxy-1,4,5-triphenyl-1,2,4-triazolium hydroxide (200, $R^1 = R^2 = R^3 = \text{Ph}$).¹³³ A general route to meso-ionic 1,2,4-triazol-3-ones (200) is exemplified by the formation of the 1,4,5-triphenyl derivative (200, $R^1 = R^2 = R^3 = \text{Ph}$) from *N*-amino-*N,N'*-diphenylbenzamidinium (202, $R^1 = R^2 = R^3 = \text{Ph}$) and phosgene.^{111,131,132,134} In contrast with this ready meso-ionic compound formation, the corresponding reaction of the *N*-methylbenzamidinium (202, $R^1 = \text{Me}$, $R^2 = R^3 = \text{Ph}$) did not yield the meso-ionic 1,2,4-triazol-3-one (200, $R^1 = \text{Me}$, $R^2 = R^3 = \text{Ph}$).¹³² The product was in fact 3,4-diphenyl-2-methyl-1,2,4-triazol-5-onium chloride (203), which on heating gave 3,4-diphenyl-1,2,4-triazol-5-one (204, $R = \text{Ph}$).¹³² The formation of the *N*-methyl derivative (200, $R^1 = \text{Me}$, $R^2 = R^3 = \text{Ph}$, yield 79%) by heating the *N*-thiobenzoyl semicarbazide (201, $R^1 = \text{Me}$, $R^2 = R^3 = \text{Ph}$, $X = \text{S}$) with potassium carbonate in methyl cyanide has been reported.¹³⁵ Another synthesis of *N*-methyl derivatives (200, $R^1 = \text{Me}$) involves methylation of 3-methyl-4-phenyl-1,2,4-triazol-5-one¹³⁶ (204,



¹³¹ K. T. Potts, S. K. Roy, and D. P. Jones, *J. Heterocycl. Chem.* **2**, 105 (1965).

¹³² (a) K. T. Potts, S. K. Roy, and D. P. Jones, *J. Org. Chem.* **32**, 2245 (1967); (b) R. Grashey and M. Baumann, *Tetrahedron Lett.*, 2947 (1972).

¹³³ G. Palazzo and L. Baiocchi, *Ann. Chim. (Rome)* **56**, 190 (1966) [*CA* **64**, 19613 (1966)]; B. Shimizu and A. Saito, *Japan Kokai* 73 62, 796 [*CA* **80**, 3533p (1974)].

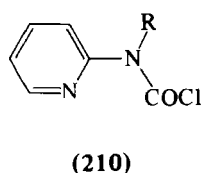
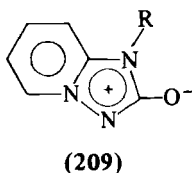
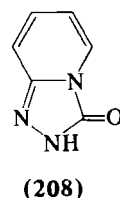
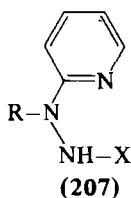
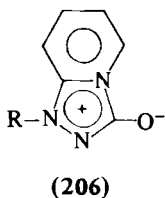
¹³⁴ S. G. Boots and C. C. Cheng, *J. Heterocycl. Chem.* **4**, 272 (1967).

¹³⁵ R. Grashey, M. Baumann, and W.-D. Lubos, *Tetrahedron Lett.*, 5877 (1968).

¹³⁶ G. Palazzo and L. Baiocchi, *Ann. Chim. (Rome)* **55**, 935 (1965) [*CA* **63**, 16335g (1965)].

R = Me). This yields a mixture including the meso-ionic compound **200**, $R^1 = R^2 = \text{Me}$, $R^3 = \text{Ph}$. The 1,3-dipolar cycloaddition of phenyl isocyanate to *N*-phenylsydnone (**205**) yielding the meso-ionic 1,4-diphenyl-1,2,4-triazol-3-one (**200**, $R^1 = R^3 = \text{Ph}$, $R^2 = \text{H}$)^{137,138} provides a comparatively rare example of the interconversion of one type of meso-ionic compound into another.

The bicyclic meso-ionic 3-oxo-1,2,4-triazolo[4,5-*a*]pyridines (**206**) have been prepared by the following methods: (i) the reaction of the hydrazines (**207**, X = H) with phosgene,^{136,139} (ii) heating the amide (**207**, X = CONH₂) or the carbamate (**207**, X = CO₂Et),¹³⁶ and (iii) alkylation or acylation of 3-oxo-1,2,4-triazolo[4,5-*a*]pyridine (**208**).¹³³ The isomeric meso-ionic 2-oxo-1,3,4-triazolo[4,5-*a*]pyridines (**209**) are formed from the carbamoyl chlorides (**210**) and sodium azide.¹⁴⁰



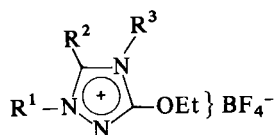
The meso-ionic 1,2,4-triazol-3-ones (**200**) are stable to acid, but alkaline hydrolysis gives 1,4-disubstituted semicarbazides. They do not normally participate in 1,3-dipolar cycloadditions,^{131,132} but the meso-ionic 1,4-diphenyl-1,2,4-triazol-3-one (**200**, $R^1 = R^3 = \text{Ph}$, $R^2 = \text{H}$) and benzyne yielded 2-phenylindazole.^{77a} 1,2,4-Triazolium salts (**211**) are formed with triethyloxonium tetrafluoroborate.⁶⁶ Reduction of the meso-ionic compound **200**, $R^1 = \text{Me}$, $R^2 = R^3 = \text{Ph}$, with lithium aluminum hydride gives the triazolidinone **212**.¹⁰⁷

¹³⁷ H. Kato, S. Sato, and M. Ohta, *Tetrahedron Lett.*, 4261 (1967).

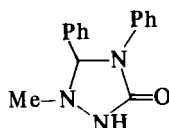
¹³⁸ M. Ota (Takeda Chem. Ind., Ltd.), Japan 70 07,741 [CA 73, 14857d (1970)].

¹³⁹ K. T. Potts, S. K. Roy, S. W. Schneller, and R. M. Huseby, *J. Org. Chem.* 33, 2559 (1968).

¹⁴⁰ G. Palazzo and L. Baiocchi, *Gazz. Chim. Ital.* 96, 1020 (1966) [CA 66, 115652u (1967)].

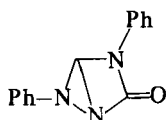


(211)

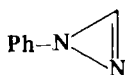


(212)

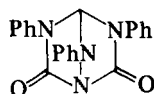
Nuclear magnetic resonance studies¹⁴¹ on meso-ionic 1,2,4-triazol-3-ones (**200**) were used to examine their relationship to the alternative 1,3,4-oxadiazol-2-imine structure (**153**). The effect of solvent polarity upon the ultraviolet spectrum of anhydro-3-hydroxy-1,4-diphenyl-1,2,4-triazolium hydroxide (**200**, $R^1 = R^3 = \text{Ph}$, $R^2 = \text{H}$) has been discussed in terms of its meso-ionic structure.¹⁴²



(213)



(214)



(215)

The photolysis of the meso-ionic 1,4-diphenyl-1,2,4-triazol-3-one (**200**, $R^1 = R^3 = \text{Ph}$, $R^2 = \text{H}$) was stated^{97a} to yield phenyl isocyanate (13%), *N,N'*-diphenylurea (23%), and the bicyclic compound **215** (49%). These results were interpreted in terms of the fragmentation of the photo-intermediate **213** yielding the *N*-phenyldiazirine (**214**).⁹⁷ A later publication by the same group^{97b} reports different results. Photolysis of meso-ionic 1,4-diphenyl-1,2,4-triazol-3-one (**200**, $R^1 = R^3 = \text{Ph}$, $R^2 = \text{H}$) was stated to yield^{97a} phenylisocyanate and the bicyclic compound **215**. Later studies^{97b} have shown that the bicyclic compound **215** is not produced by the photolysis of **200**, $R^1 = R^3 = \text{Ph}$, $R^2 = \text{H}$. Irradiation in methanol-methylene chloride gave methyl phenylcarbamate (25%), benzimidazole (18%), and azobenzene (7%).

5. 1,2,4-Triazol-3-imines (Anhydro-3-amino-1,2,4-triazolium Hydroxides) (**216**)

The meso-ionic 1,2,4-triazol-3-imines can in principle exist as isomers **216** and **217**, but only recently has a specific synthesis of these two isomers been described.¹⁴³ Aryl isocyanide dichlorides (**218**)¹⁴⁴ and

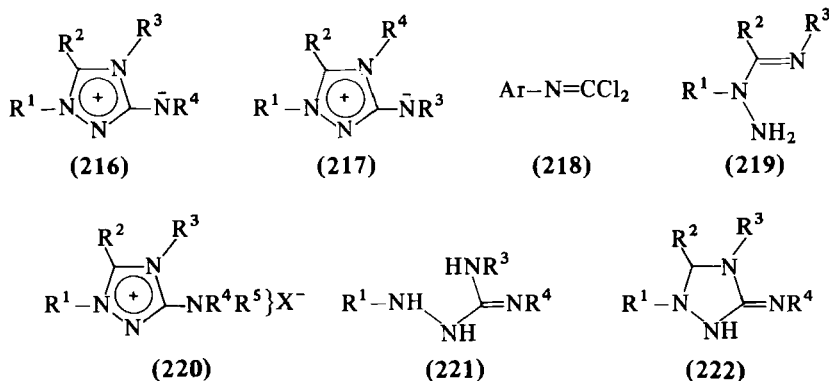
¹⁴¹ G. W. Evans and B. Milligan, *Aust. J. Chem.* **20**, 1779 (1967); R. F. Smith, J. L. Deutsch, P. A. Almeter, D. S. Johnson, S. M. Roblyer, and T. C. Rosenthal, *J. Heterocycl. Chem.* **7**, 671 (1970).

¹⁴² (a) P. B. Talukdar, S. K. Sengupta, and A. K. Datta, *Indian J. Chem.* **9**, 179 (1971) [*CA* **75**, 27561u (1971)]; (b) **9**, 1018 (1971).

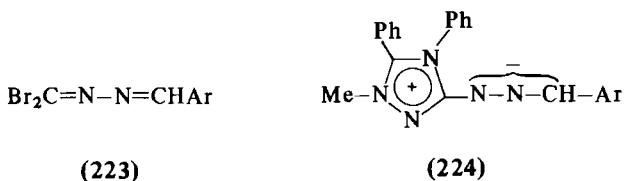
¹⁴³ W. D. Ollis and C. A. Ramsden, *Chem. Commun.*, 1224 (1971); *J. Chem. Soc., Perkin Trans. I*, 638 (1974).

¹⁴⁴ E. Kühle, B. Anders, and G. Zumach, *Angew. Chem., Int. Ed. Engl.* **6**, 649 (1967).

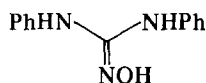
N-aminoamidines (219) in boiling toluene give the intermediate 2-arylamino-1,3,4-triazolium chlorides (220, $R^5 = H$), which with ammonium hydroxide yield the yellow crystalline meso-ionic products (216). This method has been used to synthesize pairs of isomers (216 and 217), and their equilibration ($216 \rightleftharpoons 217$) in boiling ethanol has been reported.¹⁴³ The original syntheses by Busch of the "endoiminotriazolines" later recognized as meso-ionic 1,2,4-triazol-3-imines (216 and 217)^{2b} involved either the reaction of *N*-aminoguanidines (221) with acid chlorides or the oxidation of triazolidines (222) obtained from *N*-aminoguanidines (221) and aldehydes. These two methods presumably yielded one of two possible products (216 or 217) or mixtures (216 and 217).



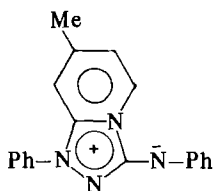
The dipole moments in benzene solution of the compounds 216, $R^1 = Me$, $R^2 = R^3 = R^4 = Ph$ ($\mu = 8.2$ D); 216, $R^1 = Me$, $R^2 = R^3 = Ph$, $R^4 = p\text{-Cl} \cdot C_6H_4$ ($\mu = 9.9$ D), and its isomer 217, $R^1 = Me$, $R^2 = R^3 = Ph$, $R^4 = p\text{-Cl} \cdot C_6H_4$ ($\mu = 8.2$ D) clearly support their meso-ionic structure.¹⁰⁸ Like the analytical reagent nitron (216, $R^1 = R^3 = R^4 = Ph$, $R^2 = H$), the meso-ionic 1,2,4-triazol-3-imines (216, $R^1 = Me$, $R^2 = Ph$, $R^3 = R^4 = Ar$, $R^5 = H$, $X = NO_3$) with dilute nitric acid. With methyl iodide they form methiodides (220, $R^1 = Me$, $R^2 = Ph$, $R^3 = R^4 = Ar$, $R^5 = Me$, $X = I$), and they are reduced to triazolidines (222, $R^1 = Me$, $R^2 = Ph$, $R^3 = R^4 = Ar$) by lithium aluminum hydride.¹⁴³



4-Aryl-1,1-dibromo-2,3-diazabutadienes (223)¹⁴⁵ and the *N*-aminoamidine (219, $R^1 = \text{Me}$, $R^2 = R^3 = \text{Ph}$) yield 1,3,4-triazolium bromides (220, $R^1 = \text{Me}$, $R^2 = R^3 = \text{Ph}$, $R^4 = \text{H}$, $R^5 = \text{N=CHAr}$), which with ammonia in chloroform solution give novel derivatives (224) of meso-ionic 1,2,4-triazol-3-imines (216). These compounds are of interest in that they belong to a new type of meso-ionic heterocycle in which the exocyclic substituent f (see Table I) is a stabilized carbanionoid residue, $\overline{\text{N-N-CHAr}}$.¹⁴⁶



(225)



(226)

An interesting rearrangement is involved in the reaction between *N*-hydroxy-*N'*,*N''* diphenylguanidine (225), toluenesulfonyl chloride, and γ -picoline in benzene at 0°. This yields a colorless toluenesulfonate which with alkali gives red anhydro-*s*-triazolo[4,3-*a*]pyridinium hydroxide (226), which is a derivative of meso-ionic 1,2,4-triazol-3-imine (216).¹⁴⁷

6. 1,2,4-Triazole-3-thiones (Anhydro-3-mercapto-1,2,4-triazolium Hydroxides) (227)

When Busch's "endo-thiotriazolines" were formulated as meso-ionic compounds,^{2b} it was recognized that two constitutional possibilities (227 or 228) required consideration. Later studies^{141,148} established that the "endo-thiotriazolines" were in fact the meso-ionic 1,2,4-triazole-3-thiones (227). Recently, a specific synthesis of their meso-ionic isomers (228) has been reported,¹⁴⁹ and under equilibration conditions in hot ethanol the rearrangement $228 \rightarrow 227$ occurs.^{149a} This explains why the meso-ionic 1,2,4-triazole-3-thiones (227) are the products of synthetic

¹⁴⁵ F. L. Scott and D. A. Cronin, *Chem. Ind. (London)*, 1757 (1964); F. L. Scott, J. A. Cronin, and J. Donovan, *Tetrahedron Lett.*, 4615 (1969).

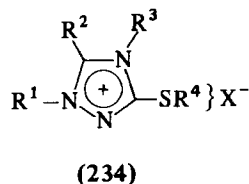
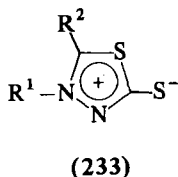
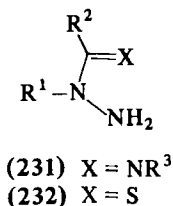
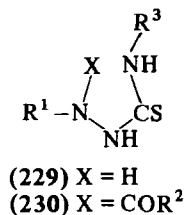
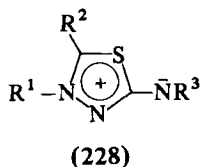
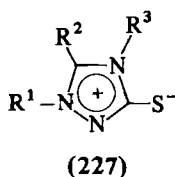
¹⁴⁶ E. Cawkill, W. D. Ollis, C. A. Ramsden, and G. P. Rowson, unpublished work.

¹⁴⁷ R. J. Grout, T. J. King, and M. W. Partridge, *Chem. Commun.*, 898 (1971).

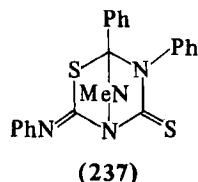
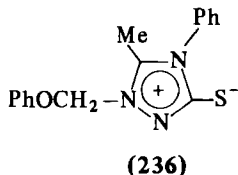
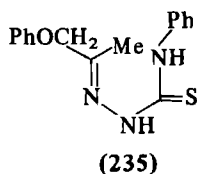
¹⁴⁸ M. Ohta, H. Kato, and T. Kaneko, *Bull. Chem. Soc. Jap.* **40**, 579 (1967).

¹⁴⁹ (a) W. D. Ollis and C. A. Ramsden, *Chem. Commun.*, 1222 (1971); *J. Chem. Soc., Perkin Trans. I*, 633 (1974); (b) P. Thieme, M. Patsch, and H. König, *Ann.* **764**, 94 (1972); H. König, P. Thieme, and A. Amann (Badische Anilin-und Soda-Fabrik A.-G.) Ger. Offen. 2,147,025 [*CA* **78**, 159618q (1973)].

routes that could, in principle, yield either the meso-ionic 1,2,4-triazole-3-thiones (227) or their isomers (228).



A number of methods are available for the synthesis of meso-ionic 1,2,4-triazole-3-thiones (227). These include (i) anhydro-acylation of 1,4-disubstituted thiosemicarbazides (229),^{2b,9b,131,132,150} (ii) heating of 4-acyl-1,4-disubstituted thiosemicarbazides (230),^{132,151} (iii) reaction of *N*-aminoamidines (231) with thiophosgene,^{9b,131,132} (iv) reaction of *N*-aminoamidines or *N*-thioacylhydrazines (232) with isothiocyanates,^{149,152} or carbon disulfide-dicyclohexylcarbodiimide,^{152b} and (v) reaction of meso-ionic 1,3,4-thiadiazoles (233), or their corresponding methiodides, with primary amines.^{2b,9b}



The oxidative cyclization of the hydrazine 235 to the meso-ionic 1,2,4-triazole-3-thione (236) is interpreted as involving a 1,2-shift of the phenoxymethyl group.¹⁵³ The isomerization 228 → 227 in boiling

¹⁵⁰ G. F. Duffin, J. D. Kendall, and H. R. J. Waddington, *J. Chem. Soc.*, 3799 (1959); P. B. Talukdar, S. K. Sengupta, and A. K. Datta, *J. Indian Chem. Soc.* **50**, 154 (1973).

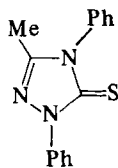
¹⁵¹ R. L. Hinman and D. Fulton, *J. Amer. Chem. Soc.* **80**, 1895 (1958).

¹⁵² (a) A. Ya. Lazaris and A. N. Egorochkin, *Zh. Org. Khim.* **6**, 2342 (1970) [*CA* **74**, 42317s (1971)]; (b) R. Grashey, M. Baumann, and R. Hamprecht, *Tetrahedron Lett.*, 2939 (1972).

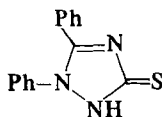
¹⁵³ J. K. Landquist, *J. Chem. Soc. C*, 323 (1970).

ethanol has been mentioned above.^{149a} This transformation (**228** \rightarrow **227**, $R^1 = \text{Me}$, $R^2 = R^3 = \text{Ph}$) may also be achieved with phenylisothiocyanate in benzene solution at room temperature and presumably involves the 1,3-dipolar cycloadduct (**237**) as an intermediate.^{149a} This 1,3-cycloaddition reaction of meso-ionic 1,3,4-thiadiazol-2-imines (**228**) contrasts with the behavior of their isomers (**227**); which do not apparently react with 1,3-dipolarophiles.¹³²

An interesting proposal has been put forward¹³² to account for an unexpected difference in the acylation reactions of 1,4-disubstituted thiosemicarbazides (**229**). The *N*-methyl derivative (**229**, $R^1 = \text{Ph}$, $R^3 = \text{Me}$) and acetic anhydride yields the expected meso-ionic product (**227**, $R^1 = \text{Ph}$, $R^2 = R^3 = \text{Me}$), whereas the corresponding reaction of the *N*-phenyl derivative (**229**, $R^1 = R^3 = \text{Ph}$) gives 1,4-diphenyl-3-methyl-1,2,4-triazoline-5-thione (**238**) rather than the expected meso-ionic isomer (**227**, $R^1 = R^3 = \text{Ph}$, $R^2 = \text{Me}$). This reaction does not involve a phenyl migration!¹³² This exclamation mark seemed to be appropriate at the time when this sentence was first written, but subsequently the proposal put forward by Potts, Roy, and Jones^{132a} for the transformation (**229**, $R^1 = R^3 = \text{Ph} \rightarrow \textbf{238}$) was shown to be incorrect. The alternative that the transformation is, in fact **229** \rightarrow **227**, $R^1 = R^3 = \text{Ph}$, $R^2 = \text{Me}$, has been clearly demonstrated by Grashey and Baumann.^{132b} Presumably the mystery^{132a} is now settled.^{132b} The latest interpretation^{132b} is in accord with the related suggestions made by Evans and Milligan^{141b} regarding the thermal dehydration product^{2b} of 1-formyl-1,4-diphenylthiosemicarbazide (**230**, $R^1 = R^3 = \text{Ph}$, $R^2 = \text{H}$).



(238)



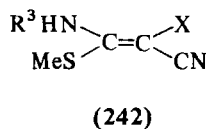
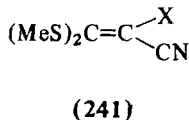
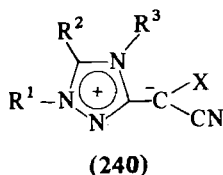
(239)

The NMR spectra¹⁴¹ and dipole moments¹⁰⁸ of 1,2,4-triazole-3-thiones support their meso-ionic formulation (**227**). For example, the compound (**227**, $R^1 = \text{Me}$, $R^2 = R^3 = \text{Ph}$) has a dipole moment of 9.1 D in dioxan solution.¹⁰⁸ The effect of solvent polarity upon the ultraviolet and visible spectra of the triphenyl derivative (**227**, $R^1 = R^2 = R^3 = \text{Ph}$) has been reported but no direct interpretation was made.¹⁴² The meso-ionic 1,2,4-triazole-3-thiones (**227**) form hydrochlorides¹³¹ (**234**, $R^4 = \text{H}$, $X = \text{Cl}$) and methiodides¹³² (**234**, $R^4 = \text{Me}$, $X = \text{I}$); they yield 1,2,4-triazolidine-3-thiones by lithium aluminum hydride reduction.^{149a}

Recently a novel member of the meso-ionic class of 1,2,4-triazole-3-thiones (227) has been described.¹⁵⁴ Heating the sodium salt, $\text{Ph-CO-NPh-NH-CS-S-CH}_2\text{-CO}_2\text{Na}$, with hydrazine gave the compound 227, $\text{R}^1 = \text{R}^2 = \text{Ph}$, $\text{R}^3 = \text{NH}_2$, which was characterized as a monobenzylidene derivative. The meso-ionic hydrazine derivative 227, $\text{R}^1 = \text{R}^2 = \text{Ph}$, $\text{R}^3 = \text{NH}_2$, undergoes an interesting reaction with nitrous acid, yielding the 1,2,4-triazoline-3-thione (239).¹⁵⁴

7. 1,2,4-Triazol-3-enes (Anhydro-3-alkyl-1,2,4-triazolium Hydroxides) (240)

These heterocycles (240) are the first representatives of meso-ionic compounds to be synthesized in which the exocyclic substituent (f, Table I) is a stabilized carbanionoid group [$-\bar{\text{C}}(\text{CN})\text{CO}_2\text{Me}$ or $-\bar{\text{C}}(\text{CN})_2$]. Their synthesis^{132b,155} involves the reaction between (i) *N*-aminoamidines (231) and bis(methylthio)acrylonitriles (241), (ii) *N*-thioacylhydrazines (232), and 3-alkylamino-3-methylthioacrylonitriles (242), and (iii) 1,2,4-triazolium iodides (234, $\text{R}^4 = \text{Me}$, $\text{X} = \text{I}$) and malononitrile.



In (240)–(242), $\text{X} = \text{CN}$ or CO_2Me

The meso-ionic 1,2,4-triazol-3-enes (240) are highly stable, colorless to greenish-yellow compounds.¹⁵⁵

H. THIADIAZOLES

1. 1,3,4-Thiadiazol-2-ones (Anhydro-2-hydroxy-1,3,4-thiadiazolium Hydroxides) (243)

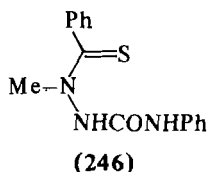
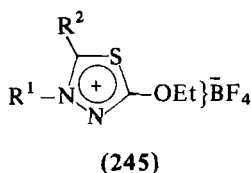
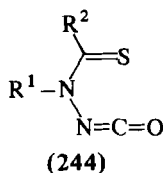
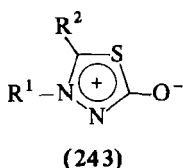
The meso-ionic 1,3,4-thiadiazol-2-ones (243) have been prepared from *N*-thioacylhydrazines (232) or their hydrochlorides^{102,103} by reaction with carbonyl chloride^{102,103,110,111,135,156} or methyl chloro-

¹⁵⁴ A. Ya. Lazaris, S. M. Shmulovich, and A. N. Egorochkin, *Zh. Org. Khim.* **8**, 2621 (1972) [*CA* **78**, 72015s (1973)].

¹⁵⁵ R. Grashey and M. Baumann, *Angew. Chem., Int. Ed. Engl.* **8**, 133 (1969).

¹⁵⁶ K. T. Potts and C. Sapino, *Chem. Commun.*, 672 (1968).

carbonate.¹³⁵ They are also formed by the isomerization of meso-ionic 1,3,4-oxadiazole-2-thiones (156).^{102,103}



Photolysis (2537 Å) in methyl cyanide solution of the compound **243**, $R^1 = \text{Me}$, $R^2 = \text{Ph}$, gives *N*-methylthiobenzamide.¹⁵⁷ This reaction has been interpreted in terms of the homolysis of the valence tautomer **244**, which has been detected spectroscopically (ν_{\max} 2260 cm^{-1} ; $\text{N}=\text{C}=\text{O}$).²² The 1,3,4-thiadiazol-2-ones have dipole moments (**243**, $R^1 = R^2 = \text{Ph}$, $\mu = 7.75$ D; **243**, $R^1 = \text{Me}$, $R^2 = \text{Ph}$, $\mu = 7.7$ D) consistent with their meso-ionic formulation.¹¹³ They react with triethyloxonium tetrafluoroborate, yielding the salts **245**.⁶⁶ The compound **243**, $R^1 = \text{Me}$, $R^2 = \text{Ph}$, and aniline gives the semicarbazide **246**.¹³⁵

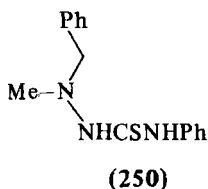
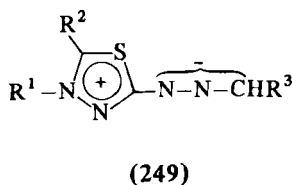
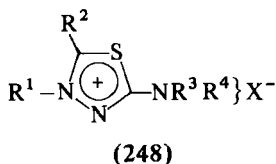
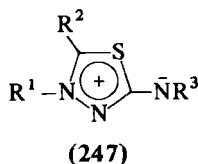
2. 1,3,4-Thiadiazol-2-imines (Anhydro-2-amino-1,3,4-thiadiazolium Hydroxides) (**247**)

The novel 1,3,4-thiadiazol-2-imines (**247**) have been prepared from *N*-thioacylhydrazines (**232**) and aryl isocyanide dichlorides ($\text{ArN}=\text{CCl}_2$).^{149a} This yields the intermediate salts (**248**) from which the meso-ionic heterocycles (**247**) are obtained as deep red oils by treatment of their chloroform solutions with anhydrous ammonia.^{149a} Analogous transformations have subsequently been achieved using similar reactions with benzoyl isocyanide dichloride ($\text{PhCON}=\text{CCl}_2$), which yield the corresponding meso-ionic 1,3,4-thiadiazol-2-imines (**247**, $R^3 = \text{Ph} \cdot \text{CO}$).^{107b} and aryl sulfonyl isocyanide dichlorides ($\text{ArSO}_2\text{N}=\text{CCl}_2$), which similarly yield the compounds **247**, $R^3 = \text{ArSO}_2$.^{107b} The corresponding reaction of *N*-thioacylhydrazines (**232**) with dibromodiazabutadienes (**223**)¹⁴⁵ has provided a new type of meso-ionic heterocycle (**249**).¹⁴⁶ Thus, within the 1,3,4-thiadiazol-2-imine class of meso-ionic heterocycle (**247**) there are four subclasses in which the exocyclic substituent (f,

¹⁵⁷ R. M. Moriarty and R. Mukherjee, *Tetrahedron Lett.*, 4627 (1969).

see Table I) may be associated with $\bar{N}-Ar$,^{149a} $\bar{N}-CO-Ar$,^{107b} $\bar{N}-SO_2-Ar$,^{107b} or $\bar{N}-N-CHAr$.¹⁴⁶ The compound **247**, $R^1 = Me$, $R^2 = R^3 = Ph$, has a dipole moment $\mu = 6.7$ D.¹⁰⁸

A second type of synthetic route to meso-ionic 1,3,4-thiadiazol-2-imines (**247**) is based on the acid-catalyzed reaction of *N*-thioacylhydrazines (**232**) with aryl isothiocyanates ($Ar-NCS$).^{152b} This reaction yields the salts (**248**) as precursors of the meso-ionic heterocycles (**247**). An interesting variant upon this route involves the reaction between *N*-thioacylhydrazines (**232**) and acyl isothiocyanates ($RCO-NCS$).^{107c, 149b} This leads to the meso-ionic heterocycles **247**, $R^3 = CO_2Et$, $CONMe_2$, $COMe$, $COCMe_3$, $COAr$, and SO_2Ph . The investigation of these compounds by X-ray photoelectron spectroscopy is a good example of the application of this physical method for the examination of meso-ionic compounds.^{149b}

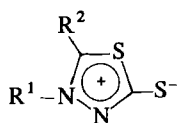


The isomerization **247** \rightarrow **227** has been discussed (see Section VII, G, 6); this type of reaction is not observed when the compound **249**, $R^1 = Me$, $R^2 = R^3 = Ph$, is heated in ethanol.¹⁴⁶ The meso-ionic 1,3,4-thiadiazol-2-imine (**247**, $R^1 = Me$, $R^2 = R^3 = Ph$) gives the methiodide (**248**, $R^1 = R^4 = Me$, $R^2 = R^3 = Ph$, $X = I$) with methyl iodide, the nitrate (**248**, $R^1 = Me$, $R^2 = R^3 = Ph$, $R^4 = H$, $X = NO_3$) with dilute nitric acid; its reduction with lithium aluminum hydride gives the thiosemicarbazide (**250**).¹⁴⁹

3. 1,3,4-Thiadiazole-2-thiones (Anhydro-2-mercapto-1,3,4-thiadiazolium Hydroxides) (**251**)

Although these substances have been known since the early investigations by Busch,^{2b, 9b} recent interest has been stimulated by their

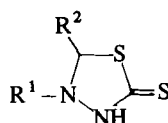
reported activity as antimicrobial agents.^{4,158-160} Methods for the synthesis of meso-ionic 1,3,4-thiadiazole-2-thiones (**251**) include reactions between (i) the salts (**252**) and acid chlorides,^{2a,9a,148,161,162} (ii) the salts (**252**) and sodium dithioformate,¹⁶² (iii) *N*-acylhydrazines or *N*-thioacylhydrazines (**232**) and carbon disulfide,^{152,163,164} (iv) *N*-thioacylhydrazines (**232**) and thiocarbonyl chloride,¹⁶⁴ (v) *N*-aminoamidines and carbon disulfide.¹⁵² Another route¹⁴⁸ to meso-ionic 1,3,4-thiadiazole-2-thiones (**251**) involves the condensation of the salts (**252**) with aldehydes giving thiadiazolidine thiones (**253**), which give disulfides (**254**) by oxidation (I_2 or $FeCl_3$). The disulfides (**254**) when heated in high-boiling solvents give the meso-ionic 1,3,4-thiadiazole-2-thiones (**251**) and thiadiazolidine thiones (**253**). The polycyclic 1,3,4-thiadiazole-2-thiones (**255**) are formed from quinoline-*N*-imides and carbon disulfide.¹⁶⁵



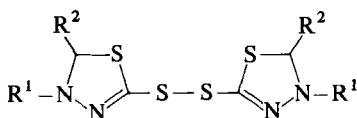
(251)



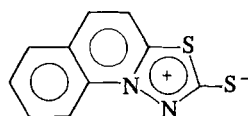
(252)



(253)



(254)



(255)

It has been shown that the transformation **254** \rightarrow **251** + **253** proceeds with first-order kinetics and that increase in solvent polarity is associated with an increase in the rate. It is proposed that the reaction involves a novel unimolecular heterolytic scission of the sulfur-sulfur bond in the symmetrical disulfide (**254**).¹⁶⁶ The kinetics of the alkaline hydrolysis of anhydro-2-mercapto-4,5-diphenyl-1,3,4-thiadiazolium

¹⁵⁸ L. B. Kier, M. C. Dodd, P. Sapko, and T. G. Stewart, *Nature (London)* **204**, 697 (1964).

¹⁵⁹ (a) T. G. Stewart and L. B. Kier, *J. Pharm. Sci.* **54**, 731 (1965); (b) J. Kuftinec and D. Kolbah, *Croat. Chem. Acta* **43**, 73 (1971).

¹⁶⁰ P. M. Weintraub and F. E. Highman, *J. Org. Chem.* **34**, 254 (1969).

¹⁶¹ W. Baker, W. D. Ollis, A. Phillips, and T. Strawford, *J. Chem. Soc.*, 289 (1951).

¹⁶² P. B. Talukdar and S. K. Sengupta, *J. Indian Chem. Soc.* **45**, 356 (1968).

¹⁶³ L. B. Kier and M. K. Scott, *J. Heterocycl. Chem.* **5**, 277 (1968).

¹⁶⁴ R. Grashey, M. Baumann, and W.-D. Lubos, *Tetrahedron Lett.*, 5881 (1968).

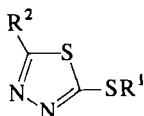
¹⁶⁵ R. Huisgen, R. Grashey, and R. Krischke, *Tetrahedron Lett.*, 387 (1962).

¹⁶⁶ A. M. Kiwan and H. M. N. H. Irving, *Chem. Commun.*, 928 (1970); *J. Chem. Soc. B*, 901 (1971).

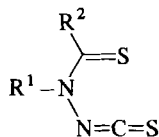
hydroxide (**251**, $R^1 = R^2 = \text{Ph}$) yielding *N*-benzoyl-*N*-phenylhydrazine has been examined: minor variants upon the well-known^{2b,9b} chemistry of meso-ionic 1,3,4-thiadiazole-2-thiones have been reported.¹⁶⁷

The dipole moments of a series of meso-ionic 1,3,4-thiadiazole-2-thiones (**251**) have been analyzed, and it has been shown that their large dipole moments are associated with a heterocyclic ring moment of 7.7 D acting at an angle of 65° to the $\text{Ph}-\text{N}$ bond direction.¹¹³ The influence of solvent polarity upon their ultraviolet spectra¹⁶⁸⁻¹⁷⁰ has been interpreted as involving an $n \rightarrow \pi^*$ transition associated with the meso-ionic structure **251**. Comparison of the ultraviolet spectra of 5-aryl derivatives (**251**, $R^2 = \text{Ar}$) indicates appreciable internuclear conjugation of the biphenyl type.¹⁶⁹ Recently the X-ray photoelectron (ESCA) spectra¹⁷¹ of two meso-ionic 1,3,4-thiadiazole-2-thiones (**251**, $R^1 = \text{Me}$, $R^2 = \text{Ph}$ and *p*-Cl. C_6H_4) have been determined.¹⁷² This important study has shown that the charge densities on the nitrogen and sulfur atoms are in satisfying accord with the charge distributions expected for the meso-ionic structure **251**.

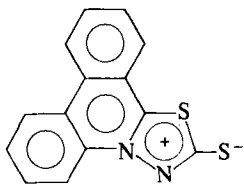
The thermal isomerization **251** \rightarrow **256** has been shown to occur in cases where $R^1 = \text{Me}$.¹⁶⁴



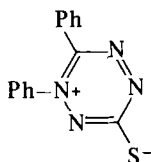
(256)



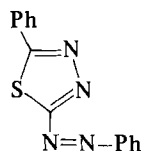
(257)



(258)



(259)



(260)

¹⁶⁷ P. B. Talukdar, S. Banerjee, and A. C. Chakraborty, *Bull. Chem. Soc. Jap.* **43**, 125 (1970); *Indian J. Chem.* **9**, 827 (1971); P. B. Talukdar, S. K. Sengupta, and A. K. Datta, *ibid.* **9**, 1417 (1971); P. B. Talukdar, S. Banerjee, and A. C. Chakraborty, *ibid.* **10**, 929 (1972); P. B. Talukdar, S. K. Sengupta, and A. K. Datta, *ibid.* **10**, 1070 (1972); **11**, 753 (1973); *J. Indian Chem. Soc.* **50**, 154 (1973).

¹⁶⁸ R. M. Moriarty, J. M. Kliegman, and R. B. Desai, *Chem. Commun.*, 1255 (1967).

¹⁶⁹ P. B. Talukdar and S. K. Sengupta, *J. Indian Chem. Soc.* **47**, 49 (1970).

¹⁷⁰ A. M. Kiwan and H. M. N. H. Irving, *J. Chem. Soc. B*, 898 (1971).

¹⁷¹ S. D. Worley, *Chem. Rev.* **71**, 295 (1971).

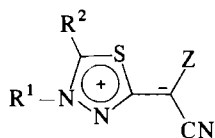
¹⁷² M. Patsch and P. Thieme, *Angew. Chem., Int. Ed. Engl.* **10**, 569 (1971).

The valence tautomerism $251 \rightleftharpoons 257$ has been proposed^{22,157} to account for the formation of *N*-methylthiobenzamide by irradiation (2537 Å) in methyl cyanide solution. The valence tautomer **257**, $R^1 = \text{Me}$, $R^2 = \text{Ph}$, has been detected spectroscopically (ν_{\max} 2060 cm^{-1} ; $-\text{N}=\text{C}=\text{S}$) either during photolysis at 25° or by heating at 160°. ²² Photochemical oxidative cyclization of 4,5-diaryl derivatives (**251**, $R^1 = R^2 = \text{Ar}$) analogous to the formation of phenanthrene from stilbene has been reported. Thus, irradiation of the 4,5-diphenyl derivative **251**, $R^1 = R^2 = \text{Ph}$, yields the tetracyclic meso-ionic compound (**258**).¹⁶⁸

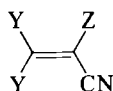
The product $\text{C}_{14}\text{H}_{10}\text{N}_4\text{S}$, obtained from the meso-ionic 1,3,4-thiadiazole-2-thione (**251**, $R^1 = R^2 = \text{Ph}$) and dimethylazodicarboxylate was initially regarded as the six-membered "meso-ionic" heterocycle **259**.¹⁷³ However, subsequent studies have established that the product is, in fact, 2-phenyl-5-phenylazo-1,3,4-thiadiazole (**260**).¹⁷⁴

4. 1,3,4-Thiadiazol-2-enes (Anhydro-2-alkyl-1,3,4-thiadiazolium Hydroxides) (**261**)

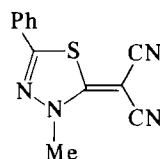
N-Thioacylhydrazines (**232**) and either 3,3-dichloroacrylonitriles (**262**, $\text{Y} = \text{Cl}$), 3,3-bis(methylthio)acrylonitriles (**262**, $\text{Y} = \text{SMe}$), or cyanomethoxycarbonylthio ketene prepared *in situ* from the dithietanone form meso-ionic 1,3,4-thiadiazol-2-enes (**261**).¹¹⁴



(261)



(262)



(263)

In (**261**) and (**262**) $\text{Z} = \text{CN}$ or CO_2Me

The orange-yellow meso-ionic thiadiazol-2-enes (**261**) are reasonably stable, but the isomerization (**261**, $R^1 = \text{Me}$, $R^2 = \text{Ph}$, $\text{Z} = \text{CN}$) \rightarrow **263** occurs at 250°. ¹¹⁴

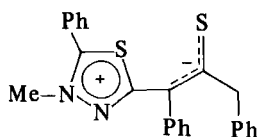
The reaction between *N*-thiobenzoyl-*N*-methylhydrazine (**232**, $R^1 = \text{Me}$, $R^2 = \text{Ph}$), and phenylthioacetylthioglycolic acid, $\text{Ph}-\text{CH}_2-\text{CS}-\text{S}-\text{CH}_2-\text{CO}_2\text{H}$, did not yield the expected product. A deep red substance, m.p. 238°–239°, has been isolated, and its X-ray crystallographic examination has shown that it has the meso-ionic structure **264**.¹⁷⁵ This

¹⁷³ R. M. Moriarty, J. M. Kliegman, and R. B. Desai, *Chem. Commun.*, 1045 (1967).

¹⁷⁴ W. L. Mosby and M. L. Vega, *Chem. Commun.*, 837 (1971); R. M. Moriarty and A. Chin, *J. Chem. Soc., Chem. Commun.*, 1300 (1972).

¹⁷⁵ R. M. Moriarty, R. Mukherjee, J. L. Flippen, and J. Karle, *Chem. Commun.*, 1436 (1971); J. L. Flippen, *Acta Crystallogr. B* **28**, 2749 (1972).

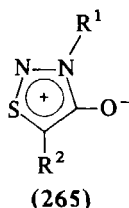
is the first example of the exocyclic group (f; Table I) being associated with the carbanionoid group, $-\text{CPh} \cdot \text{CS} \cdot \text{CH}_2\text{Ph}$.



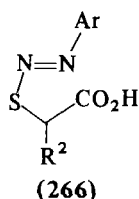
(264)

5. *1,2,3-Thiadiazol-4-ones (Anhydro-4-hydroxy-1,2,3-thiadiazolium Hydroxides) (265)*

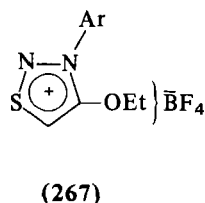
Cyclodehydration of arylazomercaptoacetic acids (266) by acetic anhydride-pyridine yields the meso-ionic 1,2,3-thiadiazol-4-ones (265, $\text{R}^1 = \text{Ar}$).¹⁷⁶⁻¹⁷⁸



(265)



(266)



(267)

The electrophilic substitution of the 3-aryl compounds (265, $\text{R}^1 = \text{Ar}$, $\text{R}^2 = \text{H}$) exemplified by the formation of 5-bromo- (265, $\text{R}^1 = \text{Ar}$, $\text{R}^2 = \text{Br}$) and 5-nitro derivatives (265, $\text{R}^1 = \text{Ar}$, $\text{R}^2 = \text{NO}_2$) has been put forward as evidence against the meso-ionic formulation 265.¹⁷⁶ This approach is unacceptable^{2b} since ground state charge distribution cannot be deduced from reaction products. The aluminum-amalgam reduction¹⁷⁹ of meso-ionic 1,2,3-thiadiazol-4-ones (265) yields either *N*-mercaptoacetyl-*N*-arylhydrazines or *N*-acyl-*N*-arylhydrazines. Triethyl-oxonium tetrafluoroborate and meso-ionic 1,2,3-thiadiazol-4-ones (265) yield 1,2,3-thiadiazolium tetrafluoroborates (267).⁶⁶ The effect of solvent on the ultraviolet spectra of meso-ionic 1,2,3-thiadiazol-4-ones (265) has been reported.¹⁸⁰

¹⁷⁶ G. F. Duffin and J. D. Kendall, *J. Chem. Soc.*, 3189 (1956).

¹⁷⁷ D. P. Cameron (Pfizer Inc.), U.S. Patent 3,580,921 [CA 75, 49095x (1971)].

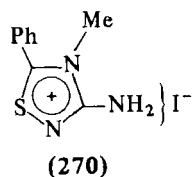
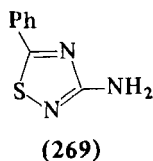
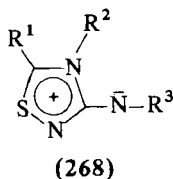
¹⁷⁸ E. H. Wiseman and D. P. Cameron, *J. Med. Chem.* 12, 586 (1969).

¹⁷⁹ W. Pacha and B. Prijs, *Helv. Chim. Acta* 41, 521 (1958).

¹⁸⁰ P. B. Talukdar, S. K. Sengupta, and A. K. Datta, *Indian J. Chem.* 9, 1018 (1971).

6. *1,2,4-Thiadiazol-3-imines (Anhydro-3-amino-1,2,4-thiadiazolium Hydroxides) (268)*

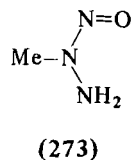
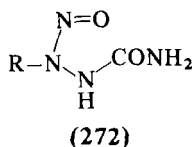
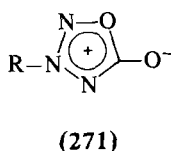
Only one representative of this class has been described.¹⁸¹ 3-Amino-5-phenyl-1,2,4-thiadiazole (269) and methyl iodide gave the iodide (270) which with silver oxide gave the meso-ionic 1,2,4-thiadiazol-3-imine (268, R¹ = Ph, R² = Me, R³ = H).¹⁸¹



I. OXATRIAZOLES

1. *1,2,3,4-Oxatriazol-5-ones (Anhydro-5-hydroxy-1,2,3,4-oxatriazolium Hydroxides) (271)*

Meso-ionic 3-alkyl-1,2,3,4-oxatriazol-5-ones (271) are obtained^{101,182,183} by the nitrosation of 1-alkyl semicarbazides, RNHNHCONH₂. At low temperatures, the intermediate *N*-nitroso derivatives (272) can be isolated, which cyclize on heating.¹⁸⁴ An alternative synthetic route is illustrated by the formation of meso-ionic 3-methyl-1,2,3,4-oxatriazol-5-one (271, R = Me) from *N*-nitroso-*N*-methylhydrazine (273) and phosgene.¹⁸⁵



Analogous routes cannot be successfully employed for the synthesis of meso-ionic 3-aryl-1,2,3,4-oxatriazol-5-ones (271). Thus, nitrosation of 1-arylssemicarbazides yields arylazocarbonamides with loss of nitroxyl.¹⁸⁶ Meso-ionic 3-aryl-1,2,3,4-oxatriazol-5-ones are formed by

¹⁸¹ J. Goerdeler and W. Roth, *Chem. Ber.* **96**, 534 (1963).

¹⁸² J. H. Boyer and F. C. Canter, *J. Amer. Chem. Soc.* **77**, 1280 (1955).

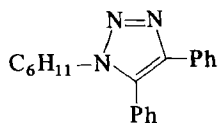
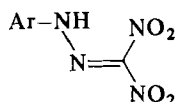
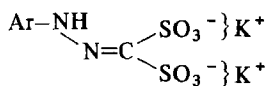
¹⁸³ T. L. Thomas, M. Fedorchuk, B. V. Shetty, and F. E. Anderson, *J. Med. Chem.* **13**, 196 (1970).

¹⁸⁴ J. H. Boyer and J. A. Hernandez, *J. Amer. Chem. Soc.* **78**, 5124 (1956).

¹⁸⁵ M. Hashimoto and M. Ohta, *Bull. Chem. Soc. Jap.* **35**, 766 (1962).

¹⁸⁶ O. Widman, *Ber.* **28**, 1925 (1895).

(i) nitrosation of potassium arylhydrazonomethane disulfonates (274),^{187,188} (ii) coupling of diazonium salts with nitroform,^{189,190} and (iii) coupling of diazonium salts with the potassium salt of dinitromethane.¹⁹¹ Reactions (ii) and (iii) presumably involve intermediates of the type 275. The addition of nitrous acid is not required because intermediate *N*-nitroso derivatives are presumably formed *in situ* by hydrolysis of the compounds 275. This view is supported by the isolation of the compound 275, Ar = *p*-O₂N.C₆H₄, and its thermal transformation into the meso-ionic derivative (271, Ar = *p*-O₂N.C₆H₄).¹⁹¹



Information concerning the chemistry of meso-ionic 3-alkyl- and 3-aryl-1,2,3,4-oxatriazol-5-ones (271) is limited, but further investigation may well be encouraged by reports of pronounced hypotensive activity.¹⁹² 3-Cyclohexyl-1,2,3,4-oxatriazol-5-one (271, R = cyclohexyl) is resistant to attack by dilute mineral acid, but warm concentrated sulfuric acid gives cyclohexanol and carbon dioxide.¹⁸⁴ In contrast, acid hydrolysis of 3-phenyl-1,2,3,4-oxatriazol-5-one (271, R = Ph) yields phenyl azide.¹⁸⁹ Meso-ionic 3-cyclohexyl-1,2,3,4-oxatriazol-5-one shows two unusual reactions: its photoirradiation in benzene gives cyclohexanone^{97a} and heating with diphenylacetylene yields 1-cyclohexyl-4,5-diphenyl-1,2,3-triazole (276)¹⁰⁴ rather than the expected 2-cyclohexyl-4,5-diphenyl-1,2,3-triazole.

The dipole moment of the *N*-phenyl derivative (271, R = Ph) in benzene solution is 6.14 D,¹⁰⁸ which may be compared with the molecular orbital calculations by Sundaram and Purcell¹⁹³ which give a value of 5.3 D for the meso-ionic 1,2,3,4-oxatriazol-5-one heterocyclic ring moment.

¹⁸⁷ H. von Pechmann, *Ber.* 29, 2161 (1896).

¹⁸⁸ W. V. Farrar, *J. Chem. Soc.*, 906 (1964).

¹⁸⁹ A. Quilico, *Gazz. Chim. Ital.* 62, 503, 912 (1932); 63, 269 (1933); A. Quilico and R. Justoni, *ibid.* 63, 862 (1933); 65, 201 (1935); A. Quilico and M. Simonetta, *ibid.* 76, 259 (1946).

¹⁹⁰ G. Ponzio, *Gazz. Chim. Ital.* 45(2), 12 (1915); 46(2), 56 (1916); 63, 471 (1933).

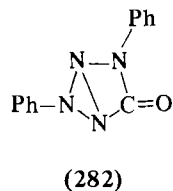
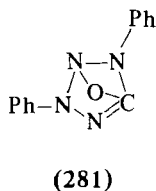
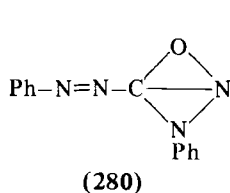
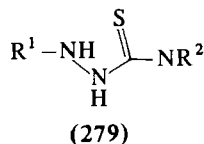
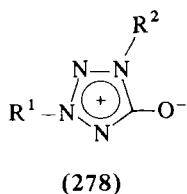
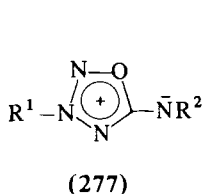
¹⁹¹ S. Hünig and O. Boes, *Ann.* 579, 28 (1953).

¹⁹² L. B. Kier, A. Al-Shamma, R. Hahn, and A. Tye, *J. Pharm. Sci.* 55, 1467 (1966); E. Tubaro, *Boll. Chim. Farm.* 105, 641 (1966) [CA 66, 17790t (1967)].

¹⁹³ K. Sundaram and W. P. Purcell, *Int. J. Quant. Chem.* 2, 145 (1968).

2. *1,2,3,4-Oxatriazol-5-imines (Anhydro-5-amino-1,2,3,4-oxatriazolium Hydroxides)* (277)

Although this was not appreciated at the time, these compounds were first handled by Busch and Becker in 1896.¹⁹⁴ Their study continued until a more extensive report by Busch and Schmidt was published in 1929.¹⁹⁵ However, Busch and his co-workers were apparently unaware of some closely related work reported by von Pechmann in 1896.¹⁸⁷ These earlier studies have been interpreted by Farrar,¹⁸⁸ extended by Christopherson and Treppendahl,¹⁹⁶ and brought to a definitive conclusion by the Sheffield group.¹⁹⁷ This history is an interesting facet of the development of the chemistry of meso-ionic heterocycles.



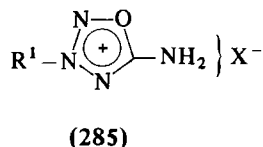
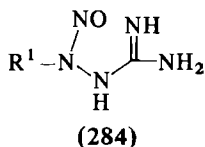
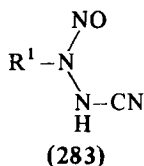
In the early investigation^{194,195} of the nitrosation of 1,4-diphenylthiosemicarbazide (279, $R^1 = R^2 = \text{Ph}$), the product was obtained as deep red needles, m.p. 110° , and was allocated the remarkable "1,3-endoxyhydrazomethylene" structure (280). Treatment of this deep red compound with warm aqueous alkali gave a colorless isomer, m.p. 157° , which was formulated as having one of the equally unacceptable structures 281 or 282.¹⁹⁵ Recent investigations^{196,197} have established that nitrosation of 1,4-diarylthiosemicarbazides (279) yield the meso-ionic 1,2,3,4-oxatriazol-5-imines (277), which are transformed by base into the meso-ionic isomers (278). These alkaline transformation products formulated as meso-ionic 1,2,3,4-tetrazol-5-ones (278) are in fact identical (see Section VII, J, 1) with substances prepared, but not formulated, by von Pechmann many years ago.¹⁸⁷

¹⁹⁴ M. Busch and J. Becker, *Ber.* **29**, 1686 (1896).

¹⁹⁵ M. Busch and W. Schmidt, *Ber.* **62**, 1449 (1929).

¹⁹⁶ C. Christopherson and S. Treppendahl, *Acta Chem. Scand.* **25**, 625 (1971).

¹⁹⁷ R. N. Hanley, W. D. Ollis, and C. A. Ramsden, *J. Chem. Soc., Perkin Trans. I*, in press (1976).

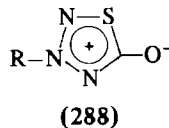
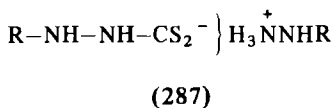
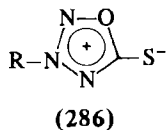


Treatment of the *N*-nitrosocyanides (283)¹⁹⁸ or the *N*-nitrosoquanylhhydrazines (284)¹⁹⁹ with hydrogen chloride yielded the 1,2,3,4-oxatriazolium chlorides (285, X = Cl), which with aqueous sodium bicarbonate gave the meso-ionic 1,2,3,4-oxatriazol-5-imines (277, R² = H).¹⁹⁸ Nitrosation of these compounds (277, R² = H) gave the interesting *N*-nitroso compounds (277, R² = NO), and acylation gave the *N*-acyl derivatives (277, R² = RCO).¹⁹⁸

Their formulation (277) as meso-ionic heterocycles is supported by their dipole moments in benzene:¹⁰⁸ 277, R¹ = R² = Ph, μ = 5.42 D; 277, R¹ = *p*-Cl . C₆H₄, R² = Ph, μ = 4.17 D; 277, R¹ = Ph, R² = *p*-Cl . C₆H₄, μ = 6.29 D. Acid hydrolysis of the diphenyl derivative (277, R¹ = R² = Ph) gives the meso-ionic 1,2,3,4-oxatriazol-5-one (271, R = Ph).¹⁹⁶ An interesting aryl group exchange is achieved by a 1,3-dipolar cycloaddition reaction between meso-ionic 1,2,3,4-oxatriazol-5-imines (277) and aryl isocyanates. Thus, the diphenyl derivative (277, R¹ = R² = Ph) and *p*-chlorophenyl isocyanate yields the product 277, R¹ = Ph, R² = *p*-Cl . C₆H₄.¹⁹⁷

3. 1,2,3,4-Oxatriazole-5-thiones (Anhydro-5-mercapto-1,2,3,4-oxatriazolium Hydroxides) (286)

Meso-ionic 3-aryl-1,2,3,4-oxatriazole-5-thiones (286) are obtained by nitrosation or aryl dithiocarbazinic acid salts (287) formed from arylhydrazines and carbon disulfide.²⁰⁰ Their meso-ionic formulation (286) is supported by their mass spectra²⁰¹ and their dipole moments: 286, R = Ph, μ = 6.83 D; 286, R = *p*-Cl . C₆H₄, μ = 5.08 D; 286, R = *p*-Me . C₆H₄, μ = 7.08 D.¹⁰⁸



¹⁹⁸ K. Masuda, T. Kamiya, and K. Kashiwa, *Chem. Pharm. Bull.* **19**, 559 (1971).

¹⁹⁹ W. G. Finnegan and R. A. Henry, *J. Org. Chem.* **30**, 567 (1965).

²⁰⁰ R. N. Hanley, W. D. Ollis, and C. A. Ramsden, *J. Chem. Soc., Chem. Commun.*, in press (1976); *J. Chem. Soc., Perkin Trans. I*, in press (1976).

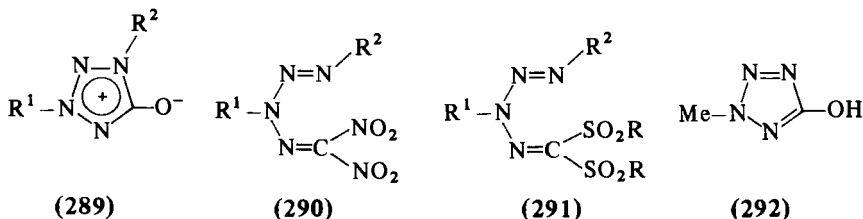
²⁰¹ W. D. Ollis and C. A. Ramsden, *J. Chem. Soc., Perkin Trans. I*, 645 (1974); R. N. Hanley, W. D. Ollis, and C. A. Ramsden, *ibid.*, in press (1976).

The meso-ionic 1,2,3,4-oxatriazoles (286)²⁰⁰ yield phenol by acidic hydrolysis, phenyl azide by alkaline hydrolysis, and the *S*-ethyl 1,2,3,4-oxatriazolium cation with triethyloxonium tetrafluoroborate. The rearrangement 286 → 288 is achieved with boiling ethanolic ammonia.

J. TETRAZOLES

1. 1,2,3,4-Tetrazol-5-ones (Anhydro-5-hydroxy-1,2,3,4-tetrazolium Hydroxides) (289)

Although representatives of this class of meso-ionic heterocycles were first prepared in 1896¹⁸⁷ and were further studied in 1929,¹⁹⁵ their formulation as meso-ionic compounds was not made until 1966,¹⁸⁸ and this was confirmed only recently by detailed study.¹⁹⁷



Mixtures of meso-ionic 1,3-diaryl-1,2,3,4-tetrazol-5-ones (289) and 1,2,3,4-oxatriazol-5-ones (271) are produced by the base-catalyzed coupling of aryl diazonium salts with dinitromethane¹⁹¹ or bisalkylsulfonylmethanes.^{191,202,203} Presumably these synthetic routes involve a Japp-Klingemann reaction²⁰⁴ leading eventually to the tetra-aza intermediates 290 and 291. The second type of synthesis¹⁹⁷ of meso-ionic 1,2,3,4-tetrazol-5-ones (289) by the rearrangement 277 → 289 with aqueous ethanolic sodium hydroxide has been discussed (Section VII, I, 2).

2-Methyl-5-hydroxytetrazole (292) and diazomethane yield 2-methyl-5-methoxytetrazole and an isomer which could be meso-ionic 1,3-dimethyl-1,2,3,4-tetrazol-5-one (289, R¹ = R² = Me).²⁰⁵ Treatment of the sweetening agent dulcin (*p*-ethoxyphenylurea) with nitrous acid gives a fluorescent product identified as the meso-ionic 1,2,3,4-tetrazol-5-one (289, R¹ = R² = *p*-EtO · C₆H₄).²⁰⁶

²⁰² H. J. Backer, *Rec. Trav. Chim. Pays-Bas* **70**, 733 (1951).

²⁰³ R. G. Dubenko, V. M. Neplyuev, and P. S. Pel'kis, *J. Org. Chem. USSR* **2**, 506 (1966) [*CA* **65**, 7085b (1966)].

²⁰⁴ R. R. Phillips, *Org. React.* **10**, 143 (1959).

²⁰⁵ K. Hattori, E. Lieber, and J. P. Horwitz, *J. Amer. Chem. Soc.* **78**, 411 (1956).

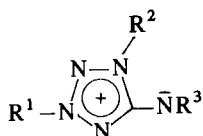
²⁰⁶ Z. Tamura, Y. Iitaka, H. Tanabe, and S. Uchiyama, *Chem. Pharm. Bull.* **18**, 2359 (1970) [*CA* **74**, 58177g (1971)].

Meso-ionic 1,2,3,4-tetrazol-5-ones (289) react with triethyloxonium tetrafluoroborate, yielding salts (294)¹⁹⁷ that react with sodium sulfide in dimethylformamide, giving meso-ionic 1,2,3,4-tetrazole-5-thiones (295).²⁰⁷

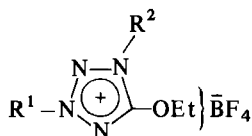
2. 1,2,3,4-Tetrazol-5-imines (Anhydro-5-amino-1,2,3,4-tetrazolium Hydroxides) (293)

The first representative of this class of meso-ionic heterocycles was the 1,3-dimethyl derivative (293, $R^1 = R^2 = \text{Me}$, $R^3 = \text{H}$) obtained by methylation of 5-amino-2-methyltetrazole with methyl benzene-sulfonate.²⁰⁸ Meso-ionic 1,2,3,4-tetrazol-5-acylimides (293, $R^1 = R^2 = \text{Me}$, $R^3 = \text{Me.CO}$, $p\text{-Me.C}_6\text{H}_4\text{.SO}_2$, $p\text{-Cl.C}_6\text{H}_4\text{.SO}_2$) have been prepared by methylation of the corresponding 1-methyltetrazole using dimethyl sulfate.^{209,210} The sequence 293, $R^1 = R^2 = \text{Me}$, $R^3 = \text{Me.CO} \rightarrow R^3 = \text{H} \rightarrow R^3 = p\text{-Me.C}_6\text{H}_4\text{SO}_2$, was achieved by acid hydrolysis followed by tosylation. The substances (293, $R^1 = R^2 = \text{Me}$, $R^3 = \text{H}$) prepared by the two routes are identical.^{208,210}

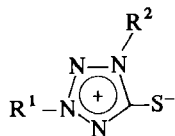
Comparison has been made²¹¹ of the relative rates of hydrolysis of the meso-ionic compounds 293, $R^1 = R^2 = \text{Me}$, $R^3 = p\text{-Me.C}_6\text{H}_4\text{.SO}_2$, and $p\text{-Cl.C}_6\text{H}_4\text{.SO}_2$, with their isomers, which can be represented by a conventional covalent structure. The meso-ionic compounds hydrolyze relatively more slowly, and this has been related to π -electron distribution.



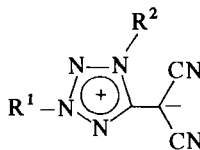
(293)



(294)



(295)



(296)

²⁰⁷ R. N. Hanley, W. D. Ollis, and C. A. Ramsden, *J. Chem. Soc., Chem. Commun.*, in press (1976); *J. Chem. Soc., Perkin Trans. I*, in press (1976).

²⁰⁸ J. H. Bryden, R. A. Henry, W. G. Finnegan, R. H. Boschan, W. S. McEwan, and R. W. Van Dolah, *J. Amer. Chem. Soc.* **75**, 4863 (1953); R. A. Henry, W. G. Finnegan, and E. Lieber, *ibid.* **76**, 2894 (1954).

²⁰⁹ V. P. Shchipanov, Y. N. Sheinker, and I. Y. Postovskii, *J. Org. Chem. USSR* **2**, 342 (1966) [*CA* **65**, 2248a (1966)].

²¹⁰ V. P. Shchipanov, *J. Org. Chem. USSR* **2**, 347 (1966) [*CA* **65**, 2248c (1966)].

²¹¹ V. P. Shchipanov, *J. Org. Chem. USSR* **2**, 1471 (1966) [*CA* **66**, 55441n (1967)].

3. *1,2,3,4-Tetrazole-5-thiones (Anhydro-5-mercapto-1,2,3,4-tetrazolium Hydroxides) (295)*

The salts (294) (Section VII, J, 1) are useful intermediates¹⁹⁷ for the preparation of other meso-ionic systems by reaction with appropriate nucleophiles. Thus, reaction with sodium sulfide in dimethyl formamide yields the 1,2,3,4-tetrazole-5-thiones (295), a new class of meso-ionic heterocycle.²⁰⁷ The 1,3-diphenyl derivative (295, $R^1 = R^2 = \text{Ph}$) has a dipole moment of 6.5 D in benzene solution in accord with its meso-ionic formulation.¹⁰⁸

4. *1,2,3,4-Tetrazol-5-enes (Anhydro-5-alkyl-1,2,3,4-tetrazolium Hydroxides) (296)*

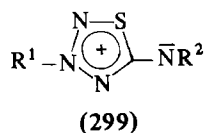
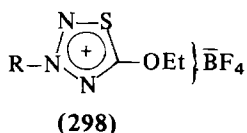
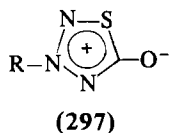
The salts (294)¹⁹⁷ with malononitrile and triethylamine in boiling acetonitrile yield the new class of meso-ionic heterocycles²¹² in which the exocyclic carbanionoid residue is a biscyanomethylene group. The diphenyl derivative (296, $R^1 = R^2 = \text{Ph}$) has a dipole moment of 9.54 D in benzene solution.¹⁰⁸

K. THIATRIAZOLES

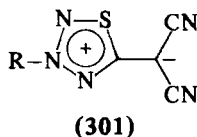
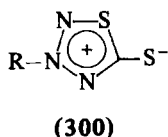
1. *1,2,3,4-Thiatriazol-5-ones (Anhydro-5-hydroxy-1,2,3,4-thiatriazolium Hydroxides) (297)*

Treatment of meso-ionic 1,2,3,4-oxatriazole-5-thiones (286) (Section VII, I, 3) with boiling ethanolic ammonia yields the isomers 297.²⁰⁰ These belong to a new class of meso-ionic heterocycle, which by *O*-alkylation with triethyloxonium tetrafluoroborate yield the salts 298.²⁰⁰ These are useful intermediates for the synthesis of a number of novel types of meso-ionic 1,2,3,4-thiatriazoles (299,²⁰⁷ 300,²⁰⁰ and 301).²¹²

The 1,2,3,4-thiatriazol-5-ones (297) have dipole moments in accord with their meso-ionic formulation.¹⁰⁸ They are remarkably stable to acidic hydrolysis, and 1,3-dipolar cycloaddition reactions have not been observed: alkaline hydrolysis yields aryl azides.



²¹² R. N. Hanley, W. D. Ollis, and C. A. Ramsden, *J. Chem. Soc., Chem. Commun.* in press (1976); *J. Chem. Soc., Perkin Trans. I*, in press (1976).



2. *1,2,3,4-Thiatriazol-5-imines (Anhydro-5-amino-1,2,3,4-thiatriazolium Hydroxides) (299)*

The salts (298)²⁰⁰ undergo a nucleophilic displacement with arylamines, yielding intermediate tetrafluoroborates, which with ethanolic sodium hydroxide yield red meso-ionic 1,2,3,4-thiatriazol-5-imines (299).²⁰⁷ The dipole moment of the diphenyl derivative in benzene is 3.7 D.¹⁰⁸

3. *1,2,3,4-Thiatriazole-5-thiones (Anhydro-5-mercapto-1,2,3,4-thiatriazolium Hydroxides) (300)*

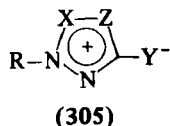
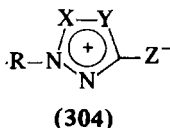
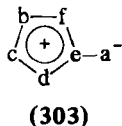
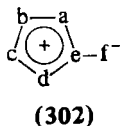
The salts (298) and sodium sulfide in dimethyl formamide yield the orange 1,2,3,4-thiatriazole-5-thiones (300).²⁰⁰

4. *1,2,3,4-Thiatriazol-5-enes (Anhydro-5-alkyl-1,2,3,4-thiatriazolium Hydroxides) (301)*

The salts (298) and malononitrile yield the orange biscyanomethylene derivatives (301). The compound 301, R = Ph, has a dipole moment of 8.84 D in benzene.²¹²

VIII. The Existence and Interconversion of Type A Meso-ionic Isomers

When the term "meso-ionic" was put forward by Baker, Ollis, and Poole in 1949,¹ the possible existence of meso-ionic isomers 302 and 303 was recognized in principle: the symbols a, b, c, d, e, and f have the same meaning as that given earlier (Section II). A typical pair of meso-ionic isomers can be more specifically represented by 304 and 305. Single compounds having the type structures 304 or 305 have been known for a number of years, but it is only recently that (i) of the existence of meso-ionic isomers 304 and 305 has been



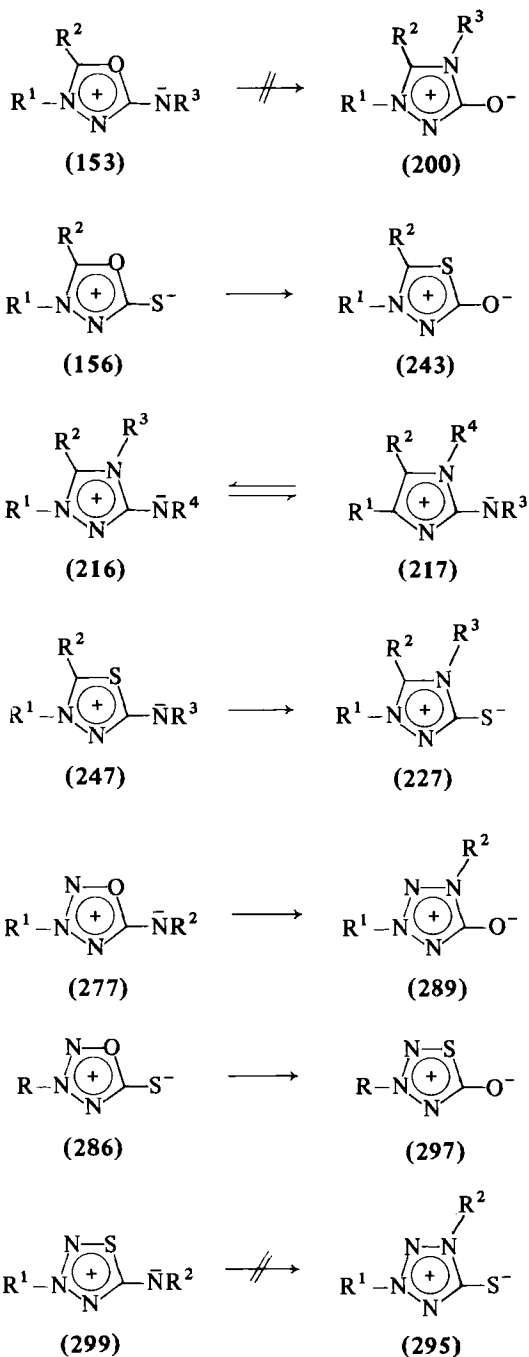


FIG. 2. Interconversion between meso-ionic isomers.

demonstrated,^{103,107,143,149,197,200,207} (ii) methods have been developed for the specific synthesis of both isomers,^{103,107,143,149,197,200,207} (iii) physical^{108,201} and chemical methods for the characterization of each isomer have been developed, and (iv) the interconversion between meso-ionic heterocyclic isomers has been studied. This has led to assessments of the relative thermodynamic stability of pairs of isomers.

Methods for the synthesis of meso-ionic isomers **304** and **305**, their characterization and interconversion have been discussed in appropriate sections of the review. These results are summarized in Fig. 2, and in order to assist in the location of compounds they are associated with the formula numbers used in the text.

In Fig. 2, the results of equilibration studies are indicated. In only one case (**216** \rightleftharpoons **217**), as might be expected, is an equilibrium established, and there is little difference in the relative thermodynamic stability of the two isomers (**216** and **217**). On current knowledge, it is not possible to provide a well-based understanding of the factors that determine the relative thermodynamic stability of meso-ionic isomers.

Various methods and reagents have been used to effect the interconversion between meso-ionic isomers **304** \rightleftharpoons **305** including (i) heating in protic solvents such as ethanol or ethyl mercaptan,^{103,143,149} (ii) treatment with hot ethanolic ammonia or ethanolic sodium hydroxide,^{197,200} (iii) heating,¹⁴⁹ (iv) heating with aryl isocyanates¹⁹⁷ or isothiocyanates.¹⁴⁹

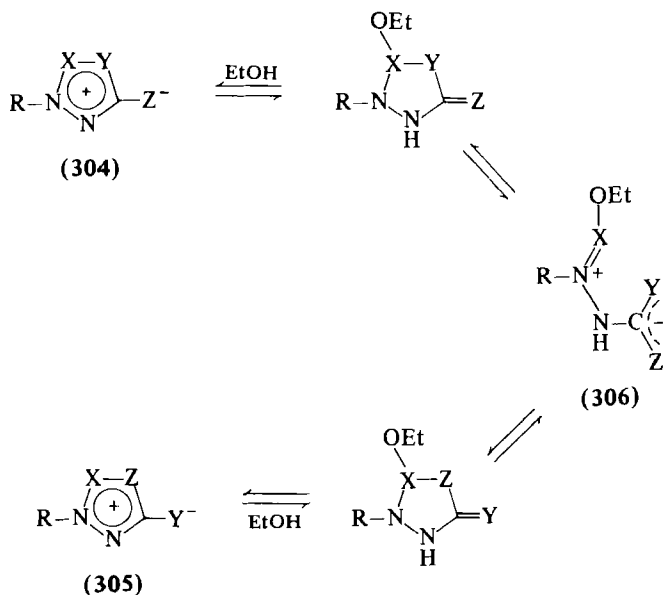
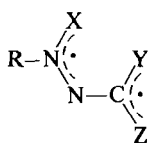
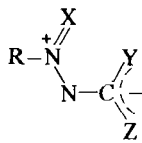


FIG. 3. Equilibration of meso-ionic isomers in protic solvents (e.g., EtOH) involving a betaine intermediate.

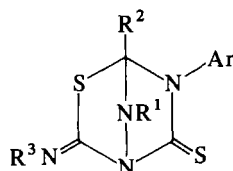
Mechanisms that are probably associated, respectively, with these processes are (i) the formation of betaine intermediates (306) (Fig. 3),^{103,143,149,197,200} (iii) homolysis or heterolysis of the X—Z bond (304) or the X—Z bond (305) giving diradical (307) or dipolar (308) intermediates, (iv) 1,3-dipolar cycloaddition yielding intermediate adducts (e.g., 309).^{149,197} The base-catalyzed rearrangements (ii) present very interesting mechanistic problems suitable for speculation and experimental enquiry.



(307)

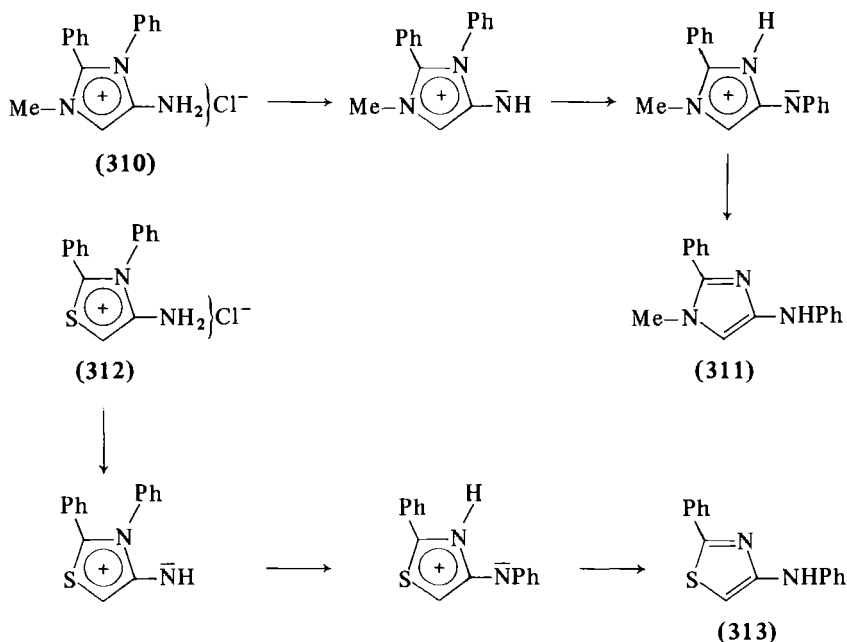


(308)



(309)

Two rearrangements may well be regarded as further examples of interconversion between meso-ionic isomers. The 1,3-diazolium chloride (310) and warm dilute aqueous potassium hydroxide yield 4-anilino-1-methyl-2-phenylimidazole (311), presumably via the indicated meso-ionic intermediates.⁶⁰ The transformation 312 → 313 by treatment of the thiazolium chloride with warm aniline may be similarly interpreted.⁸⁷



The example⁶² claimed for the acid-catalyzed rearrangement **103** \rightarrow **108** (Section VII, C, 2) has not been confirmed.^{59a,67b} the meso-ionic 1,3-thiazol-5-imines (**108**) apparently await synthesis.

The most clear-cut distinction between the pairs of meso-ionic isomers given in Fig. 2 is provided by comparison of their mass spectral fragmentation patterns.²⁰¹ Comparison of the dipole moments of corresponding isomers is also informative.¹⁰⁸

IX. Photochemistry of Type A Meso-ionic Heterocycles

The investigation of the photochemistry of meso-ionic heterocycles is still rather limited. However, some common mechanistic features can be appreciated in the pathways that have been put forward to account for the products of a number of photoreactions. A summary of the results obtained for various classes of meso-ionic heterocycles follows. Although the decision has been taken not to discuss in detail in this review the general chemistry of sydnones (**1**) and sydnone imines (**2**), it is nevertheless appropriate to include in this section the results obtained in the study of their photochemistry.

a. *1,2,3-Oxadiazol-5-ones* (Sydnones) (**1**). Irradiation of *N*-phenylsydnone (**1**, $R^1 = \text{Ph}$, $R^2 = \text{H}$) in benzene has yielded a complex mixture of photolysis products from which 4-phenyl- Δ^2 -1,3,4-oxadiazolin-5-one (**317**, $R^1 = \text{Ph}$, $R^2 = \text{H}$) has been isolated.²¹³ The mechanism proposed for this transformation²¹³ is given in Fig. 4. Postulated intermediates include the bicyclic photoisomer (**314**, $R^1 = \text{Ph}$, $R^2 = \text{H}$), the 1*H*-diazirine (**315**, $R^1 = \text{Ph}$, $R^2 = \text{H}$), and the 1,3-dipolar nitrilimine (**316**, $R^1 = \text{Ph}$, $R^2 = \text{H}$). In connection with this proposal, it has been shown²¹³ that when the irradiation of *N*-phenylsydnone (**1**, $R^1 = \text{Ph}$, $R^2 = \text{H}$) in dioxan is carried out in the presence of ¹⁴C-labeled carbon dioxide, then the radiolabel is incorporated (80% activity of the photolysis products) into the 4-phenyl- Δ^2 -1,3,4-oxadiazolin-5-one (**317**, $R^1 = \text{Ph}$, $R^2 = \text{H}$). Furthermore, the yield of this compound (**317**, $R^1 = \text{Ph}$, $R^2 = \text{H}$) is related to the pressure of externally supplied carbon dioxide.

The photochemistry of *NC*-diphenylsydnone (**1**, $R^1 = R^2 = \text{Ph}$) has been the subject of almost simultaneous study by a number of groups.²¹⁴⁻²¹⁷ Some variations of isolated reaction products occurred, but the formation of 2,4,5-triphenyl-1,2,3-triazole (**320**, $R^1 = R^2 = \text{Ph}$)

²¹³ C. H. Krauch, J. Kuhls, and H.-J. Piek, *Tetrahedron Lett.*, 4043 (1966).

²¹⁴ Y. Huseya, A. Chinone, and M. Ohta, *Bull. Chem. Soc. Jap.* **44**, 1667 (1971).

²¹⁵ C. S. Angadiyavar and M. V. George, *J. Org. Chem.* **36**, 1589 (1971).

²¹⁶ M. Märky, H.-J. Hansen, and H. Schmid, *Helv. Chim. Acta* **54**, 1275 (1971).

²¹⁷ H. Gotthardt and F. Reiter, *Tetrahedron Lett.*, 2749 (1971).

(yield 13–24%) was generally observed: this has been interpreted (Fig. 4) as involving the dimerization of the nitrilimine (**316**). Depending on the reaction conditions, other products obtained from the photolysis of *NC*-diphenylsydnone (**1**, $R^1 = R^2 = \text{Ph}$) included benzilosazone²¹⁵ and

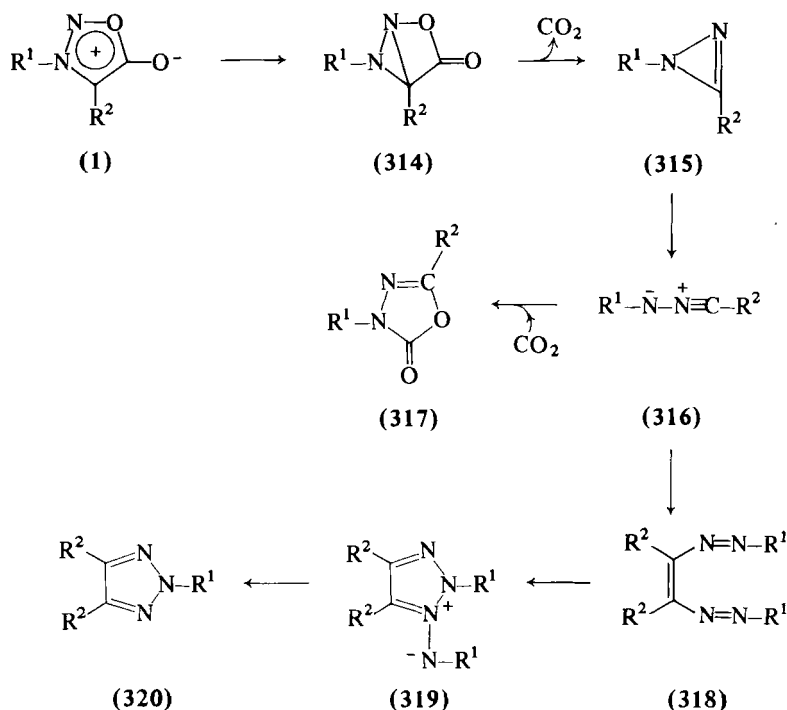


FIG. 4. Photochemistry of sydnone (1).

benzanilide.²¹⁵ It has been suggested²¹⁵ that benzanilide is formed by the hydrolysis of an amidine generated from the nitrilimine (316) and aniline.

Irradiation of *N*-cyclohexyl-*C*-phenylsydnone²¹⁸ (**1**, R¹ = cyclohexyl, R² = phenyl) in benzene under a nitrogen atmosphere gave the 1,3,4-oxadiazolin-5-one (**317**, R¹ = cyclohexyl, R² = phenyl; 15%), the bisazoethylene (**318**, R¹ = cyclohexyl, R² = phenyl; 15%), and the triazole (**320**, R¹ = cyclohexyl, R² = phenyl; 12%). When the nitrogen atmosphere was replaced by carbon dioxide, then the yield of the 1,3,4-oxadiazolin-5-one was increased from 15% to 47%. These results²¹⁸ provide good support for the general mechanistic proposals given in Fig. 4.

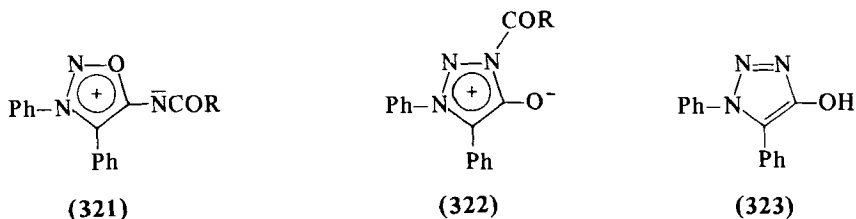
²¹⁸ Y. Huseya, A. Chinone, and M. Ohta, *Bull. Chem. Soc. Jap.* **45**, 3202 (1972).

Photochemical cycloaddition reactions²¹⁴⁻²¹⁸ between sydnones (1) and 1,3-dipolarophiles take place to give products which are different from, but isomeric with, the thermal 1,3-dipolar cycloaddition products.³ These results are directly interpreted in terms of reactions between the 1,3-dipolarophiles and the nitrilimine (316). The photochemical reactions between sydnones and the following 1,3-dipolarophiles have been reported: dicyclopentadiene,²¹⁴ dimethyl acetylene dicarboxylate,²¹⁵⁻²¹⁸ dimethyl maleate,²¹⁵ dimethyl fumarate,²¹⁵ indene,²¹⁶ carbon dioxide,²¹³ and carbon disulfide.²¹⁷

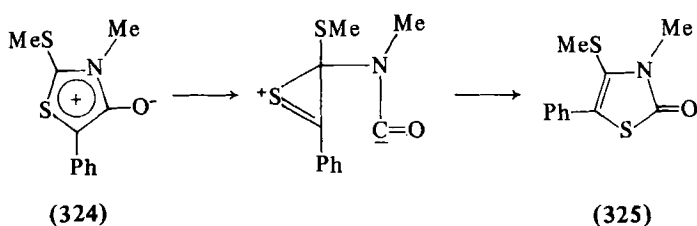
b. *1,2,3-Oxadiazol-5-imines (N-Acylsydnone Imines)* (2, $R^3 = \text{COR}$). The photochemical isomerization of *N*-acylsydnone imines (2, $R^3 = \text{COR}$) to give meso-ionic 1,2,3-triazol-4-ones (176) has been reported.^{128b}

Irradiation in benzene-ethanol of the *N*-acylsydnone imine 321, $R = \text{Me}$, yielded the isomer 322, $R = \text{Me}$ (11%), and the triazole 323 (10%). The *N*-benzoyl derivative 321, $R = \text{Ph}$, similarly yielded the isomer 322, $R = \text{Ph}$ (2%) and the triazole 323 (35%).

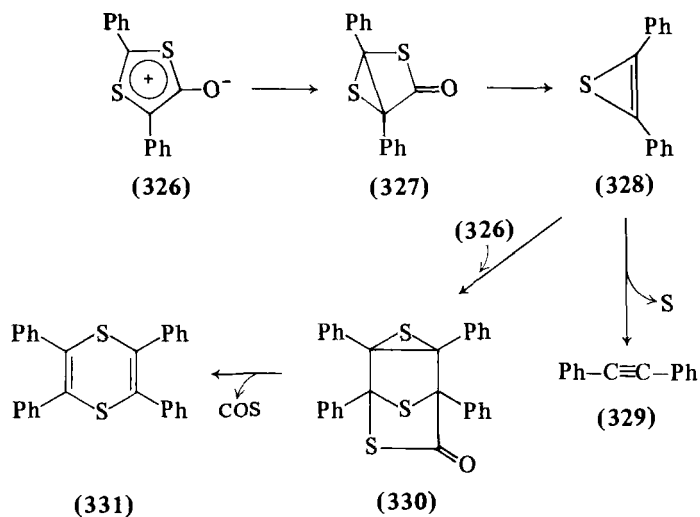
These results are curious in that the photochemistry of *N*-acylsydnone imines is quite different in mechanistic form from that of sydnones (Fig. 4) and other meso-ionic heterocycles.



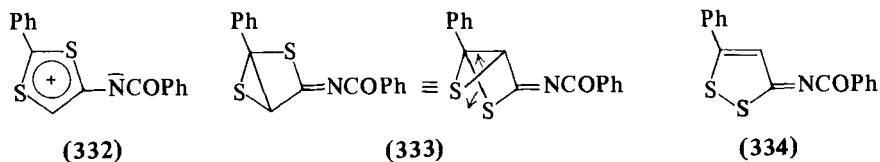
c. *1,3-Thiazol-4-ones* (114). Irradiation, in ethanol, of the meso-ionic 1,3-thiazol-4-one (324) yields the isomeric 3-methyl-4-methylthio-5-phenyl-1,3-thiazol-2-one (325).^{78b} The rather curious mechanism that has been proposed^{78b} for the rearrangement $324 \rightarrow 325$ is given below.



d. *1,3-Dithiol-4-ones* (134). Photolysis of 2,5-diphenyl-1,3-dithiol-4-one (326) yields tetraphenyl-1,4-dithiin (331; 19%), diphenylacetylene (329; 16%), and sulfur (15%).⁹⁵ These transformations have been interpreted⁹⁵ in terms of a diphenylthiiren intermediate (328).



e. *1,3-Dithiol-4-imines* (141). Irradiation of a benzene solution of the meso-ionic *N*-benzoyl-2-phenyl-1,3-dithiol-4-imine (332) gave the isomer 334 in high yield (80%).⁹⁷ The isomerization has been interpreted⁹⁷ as involving rearrangement of the bicyclic photoisomer 333.



f. *1,3,2-Oxathiazol-5-ones* (169). Photolysis, in ether-methylene chloride solution, of the meso-ionic 4-phenyl-1,3,2-oxathiazol-5-one (335) gave benzonitrile (77%) and sulfur (91%).¹¹⁸ This result has been interpreted¹¹⁸ in terms of elimination of carbon dioxide from the photoisomer (336) yielding the thiazirin (337) which after isomerization to benzonitrile sulfide disproportionates, giving benzonitrile and sulfur. The intermediate benzonitrile sulfide has been trapped^{118a} with dimethyl acetylene dicarboxylate, giving the products 338 and 339.

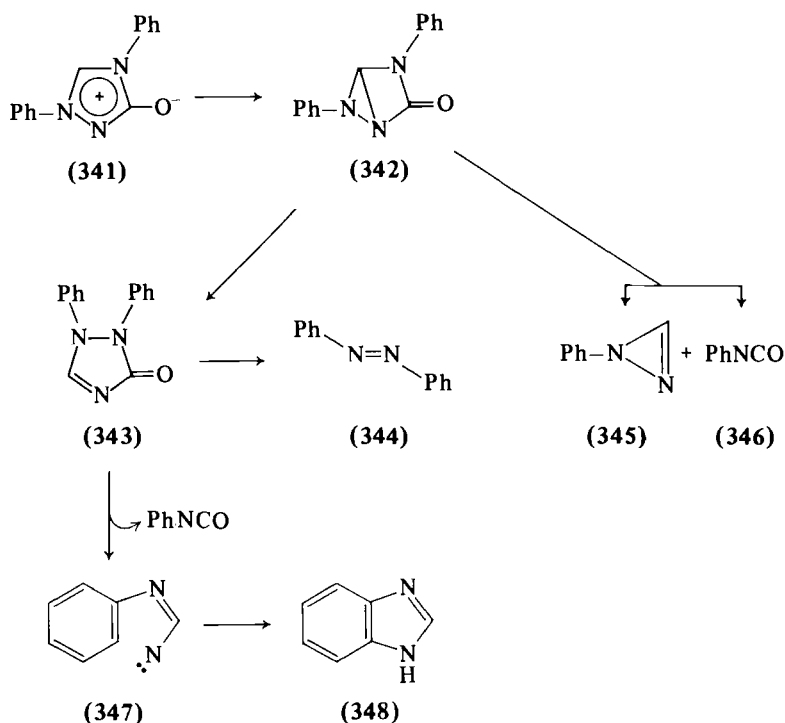
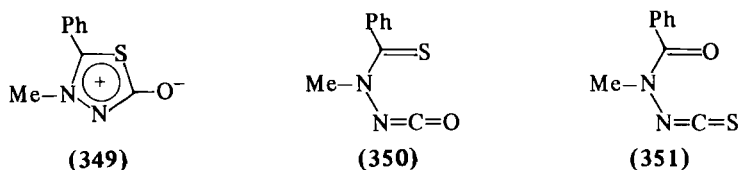


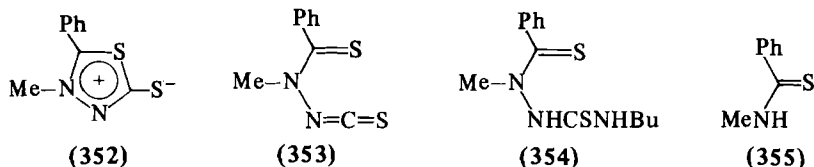
FIG. 6. Photochemistry of 1,2,4-triazol-3-ones.

phenylisocyanate (346), and benzimidazole (348). Two possible routes from the bicyclic photoisomer (342) have been suggested. One route⁹⁷ involves its photocleavage to *N*-phenyl-1*H*-diazirine (345) and phenylisocyanate. The second route^{97b} involves the valence isomerization $342 \rightarrow 343$ which could then fragment yielding azobenzene (344), phenylisocyanate, and phenyliminomethyl nitrene (347)—a reasonable precursor of benzimidazole (348).

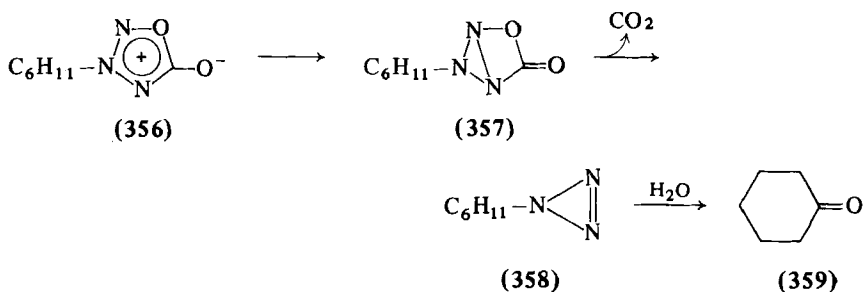
h. *1,3,4-Thiadiazol-2-ones* (243). Irradiation of the meso-ionic 1,3,4-thiadiazol-2-one (349) in methyl cyanide solution gives the *N*-isocyanate (350) (ν_{\max} 2060 cm^{-1}) and *N*-isothiocyanate (351) (ν_{\max} 2260 cm^{-1}), which were both recognized spectroscopically.²² Mechanisms for the conversion $350 \rightarrow 351$ have been considered.²²



i. *1,3,4-Thiadiazole-2-thiones* (251). Irradiation^{22,157} in methyl cyanide solution of the compound **352** yields the valence tautomer **353**. This has been recognized spectroscopically²² and by trapping with *n*-butylamine, which yields the thiourea (**354**).²² Further photofragmentation of the *N*-isothiocyanate (**353**) yielded the thioamide (**355**) and elemental sulfur.



j. *1,2,3,4-Oxatriazol-5-ones* (271). Photolysis^{97a} of the *N*-cyclohexyl derivative (**356**), followed by hydrolysis, yields cyclohexanone. This has been interpreted in terms of the following sequence: **356** → **357** → **358** → **359**.



k. *General Comments*. Meso-ionic heterocycles show several general types of photochemical transformation. These can be summarized (Fig. 7) as (i) a valence tautomerism giving the heterocumulene **364**, (ii) a valence isomerization giving the isomer **365**, and (iii) a fragmentation reaction giving three-membered heterocycles (**362**) which could be the precursors of 1,3-dipoles (**366**). These transformations have usually been interpreted in terms of a bicyclic photoisomer (**361**).

The suggestion that three-membered heterocycles (**362**) are involved is illustrated by the postulated generation of derivatives of 1*H*-diazirine (**315** and **345**), thiiren (**328**), thiazirin (**337**), and 1*H*-triazirine (**358**). These three-membered heterocycles belong to the class of 4π-antiaromatic heterocycles; their possible rôle as reaction intermediates²¹⁹ is of general interest. There is, however, an interesting difference between the photochemistry of sydnone (Fig. 4) and meso-ionic 1,2,4-triazol-3-ones (Fig. 6). In both cases 1*H*-diazirines (**315** and

²¹⁹ M. J. S. Dewar and C. A. Ramsden, *J. Chem. Soc., Chem. Commun.*, 688 (1973).

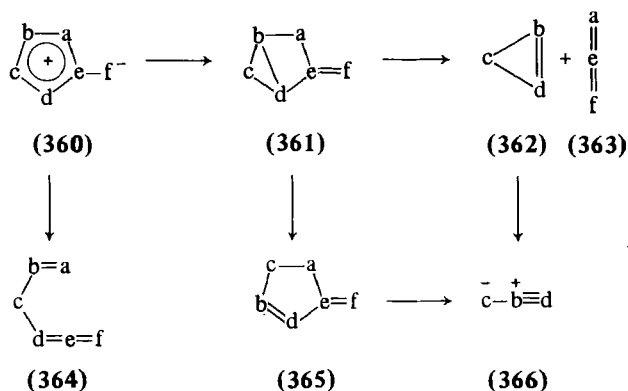


FIG. 7. Photochemical transformations of meso-ionic heterocycles.

345) have been considered²¹³⁻²¹⁸ as possible intermediates, whereas there is no experimental evidence^{97b} that supports the view that 1*H*-diazirines could be involved as intermediates in the photochemical reactions of sydnones (Fig. 4) and meso-ionic 1,2,4-triazol-3-ones (Fig. 6).

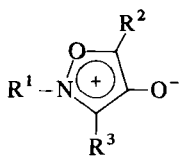
X. The Chemistry of Meso-ionic Compounds of Type B

These are listed under the parent heterocyclic systems in the order given in Table II (Section V).

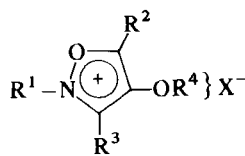
A. OXAZOLES

1. 1,2-Oxazol-4-ones (Anhydro-4-hydroxy-1,2-oxazolium Hydroxides) (367)

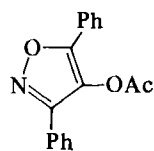
Attempts to prepare meso-ionic 1,2-oxazol-4-ones (**367**) have not been successful, although the corresponding salts (**368**) have been isolated. Treatment of the salts (**368**) with basic reagents may have yielded 1,2-oxazol-4-ones (**367**), but these could not be isolated.



(367)



(368)

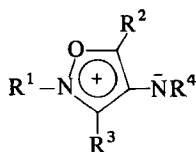


(369)

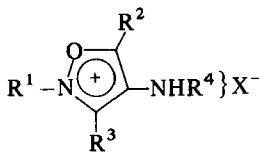
4-Acetoxy-3,5-diphenylisoxazole (369)²²⁰ was *N*-alkylated with triethyloxonium tetrafluoroborate giving the salt 368, $R^1 = \text{Et}$, $R^2 = R^3 = \text{Ph}$, $R^4 = \text{Ac}$, $X = \text{BF}_4$.²²¹ The salt 368, $R^1 = \text{Me}$, $R^2 = R^3 = \text{Ph}$, $R^4 = \text{H}$, $X = \text{ClO}_4$, was similarly prepared using methyl fluorosulfonate followed by perchloric acid.²²² It is concluded that the spectrum of the salt 368, $R^1 = \text{Me}$, $R^2 = R^3 = \text{Ph}$, $R^4 = \text{H}$, $X = \text{ClO}_4$, in alkaline solution is that of its decomposition products, but a transient yellow color may be due to the meso-ionic 1,2-oxazol-4-one (367, $R^1 = \text{Me}$, $R^2 = R^3 = \text{Ph}$).²²²

2. 1,2-Oxazol-4-imines (Anhydro-4-amino-1,2-oxazolium Hydroxides) (370)

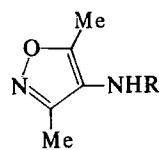
The formation of an *N*-tosyl derivative of a meso-ionic 1,2-oxazol-4-imine (370) in solution is possible, but the product was not isolated.



(370)



(371)



(372)

4-Amino-3,5-dimethylisoxazole (372, $R = \text{H}$)²²³ gave an *N*-tosyl derivative (372, $R = \text{tosyl}$), which by treatment with methyl fluorosulfonate followed by perchloric acid gave the salt 371, $R^1 = R^2 = R^3 = \text{Me}$, $R^4 = \text{tosyl}$, $X = \text{ClO}_4$.²²² Attempts to isolate the meso-ionic sulfonamidate (370, $R^1 = R^2 = R^3 = \text{Me}$, $R^4 = \text{tosyl}$) by treatment of the salt with potassium hydroxide or triethylamine were unsuccessful, but spectroscopic evidence for its formation in solution has been offered.²²²

B. DIAZOLES

1. 1,2-Diazol-4-ones (Anhydro-4-hydroxy-1,2-diazolium Hydroxides) (373)

Meso-ionic 1,2-diazol-4-ones (373) were possibly first prepared in 1900 by Wolff and Fertig;²²⁴ compounds of this type (373) were again

²²⁰ A. H. Blatt and W. L. Hawkins, *J. Amer. Chem. Soc.* **56**, 2190 (1934).

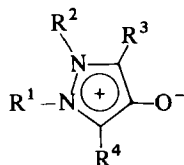
²²¹ G. Bianchi, M. J. Cook, and A. R. Katritzky, *Tetrahedron* **27**, 6133 (1971).

²²² G. V. Boyd and T. Norris, *J. Chem. Soc., Perkin Trans. I*, 1028 (1974).

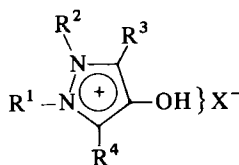
²²³ G. T. Morgan and H. Burgess, *J. Chem. Soc.* **119**, 697 (1921).

²²⁴ L. Wolff and E. Fertig, *Ann.* **313**, 12 (1900).

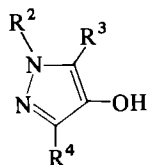
possibly encountered in 1931.²²³ The products obtained in these two studies were not structurally formulated, but the quoted molecular formulae^{224,225} match either the monohydrates of the meso-ionic heterocycles (373) or the onium hydroxides (374, X = OH). The synthesis and characterization of the meso-ionic 1,2-diazol-4-ones (373) have been recently described.^{226,227}



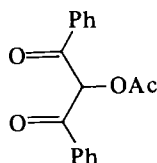
(373)



(374)



(375)



(376)

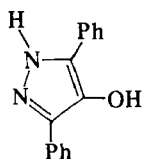
4-Hydroxy-1-phenylpyrazole (375, $R^2 = \text{Ph}$, $R^3 = R^4 = \text{H}$) yields a methiodide (374, $R^1 = \text{Me}$, $R^2 = \text{Ph}$, $R^3 = R^4 = \text{H}$, $X = \text{I}$), which with silver oxide gives a product, $\text{C}_{10}\text{H}_{12}\text{N}_2\text{O}_2$, m.p. $132^\circ\text{--}135^\circ$, which may now be formulated either as a monohydrate of the heterocycle 373, $R^1 = \text{Me}$, $R^2 = \text{Ph}$, $R^3 = R^4 = \text{H}$, or as the 1,2-diazolium hydroxide 374, $R^1 = \text{Me}$, $R^2 = \text{Ph}$, $R^3 = R^4 = \text{H}$, $X = \text{OH}$.²²⁴ 1-Phenyl-4-hydroxy-5-methylpyrazole (375, $R^2 = \text{Ph}$, $R^3 = \text{Me}$, $R^4 = \text{H}$) similarly yielded $\text{C}_{11}\text{H}_{14}\text{N}_2\text{O}_2$ (373 monohydrate, $R^1 = R^3 = \text{Me}$, $R^2 = \text{Ph}$, $R^4 = \text{H}$, or 374, $R^1 = R^3 = \text{Me}$, $R^2 = \text{Ph}$, $R^4 = \text{H}$).²²⁵

The compound 373, $R^1 = R^2 = \text{Me}$, $R^3 = R^4 = \text{Ph}$, has been prepared by two routes.^{226,227} Reaction of *N*-methylhydrazine with 2-acetoxy-1,3-diphenylpropane-1,3-dione (376) gave 4-hydroxy-1-methyl-3,5-diphenylpyrazole (375, $R^2 = \text{Me}$, $R^3 = R^4 = \text{Ph}$), which with dimethyl sulfate gave the methosulfate salt 374, $R^1 = R^2 = \text{Me}$, $R^3 = R^4 = \text{Ph}$, $X = \text{MeSO}_4$. This salt and alkali gave the meso-ionic 1,2-diazol-4-one (373, $R^1 = R^2 = \text{Me}$, $R^3 = R^4 = \text{Ph}$). Alternatively, *N,N'*-dimethylhydrazine and the dione 376, followed by treatment with alkali, gave the same compound (373, $R^1 = R^2 = \text{Me}$, $R^3 = R^4 = \text{Ph}$) directly.

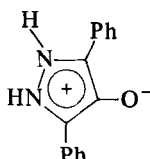
²²³ F. D. Chattaway and H. Irving, *J. Chem. Soc.*, 786 (1931).

²²⁶ M. J. Nye, M. J. O'Hare, and W.-P. Tang, *Abstr. 3rd Int. Congr. Heterocycl. Chem.*, B, p. 514 (1971).

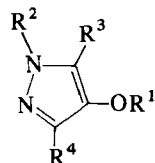
²²⁷ M. J. Nye and W.-P. Tang, *Tetrahedron* 28, 455 (1972).



(377)

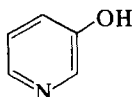


(378)

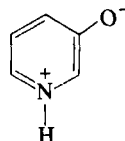


(379)

The equilibrium between the pyrazole **377** and its meso-ionic tautomer (**378**) in 4% methanol–water has been determined.²²⁸ The equilibrium is strongly in favor ($K = 3.2 \times 10^{-5}$; $\Delta F = 6.15$ kcal/mole) of the pyrazole (**377**). This result provides an instructive contrast with the approximate 1 : 1 equilibrium ratio between 3-hydroxypyridine (**380**) and its betaine tautomer (**381**) in aqueous solution.²²⁹



(380)



(381)

On heating, the meso-ionic 1,2-diazol-4-one (**373**, $R^1 = R^2 = \text{Me}$, $R^3 = R^4 = \text{Ph}$) is transformed into the isomeric ether (**379**, $R^1 = R^2 = \text{Me}$, $R^3 = R^4 = \text{Ph}$) and the 4-hydroxypyrazole (**375**, $R^2 = \text{Me}$, $R^3 = R^4 = \text{Ph}$).²²² A mechanistically analogous reaction takes place between the meso-ionic 1,2-diazol-4-one (**373**, $R^1 = R^2 = \text{Me}$, $R^3 = R^4 = \text{Ph}$) and dimethyl acetylene dicarboxylate, giving the ether **379**, $R^1 = \text{C}(\text{CO}_2\text{Me})=\text{CH}(\text{CO}_2\text{Me})$, $R^2 = \text{Me}$, $R^3 = R^4 = \text{Ph}$.²²²

Anhydro-1,2-dimethyl-3,5-diphenyl-4-hydroxy-1,2-diazolium hydroxide (**373**, $R^1 = R^2 = \text{Me}$, $R^3 = R^4 = \text{Ph}$) shows a band (1546 cm^{-1} in dimethyl sulfoxide), which has been assigned as a carbonyl band.²³⁰ This absorption band, which is much lower than, for example, the sydnone (**1**) ($\nu_{\text{CO}} 1750\text{--}1770 \text{ cm}^{-1}$)⁷ has been briefly considered in relation to the electronic characteristics of type A and type B meso-ionic heterocycles.²³⁰ However, the significance of this spectral difference must surely await more extensive comparison between corresponding type A and type B heterocycles. The compound (**373**, $R^1 = R^2 = \text{Me}$, $R^3 = R^4 = \text{Ph}$) also shows a striking solvent dependence of its ultraviolet/visible spectrum (λ_{max} C_6H_6 447; Me_2SO 421; CHCl_3 410; Bu_2OH 370; MeOH 345; H_2O 325 nm).²³⁰

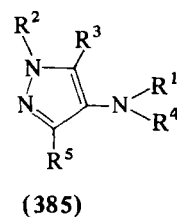
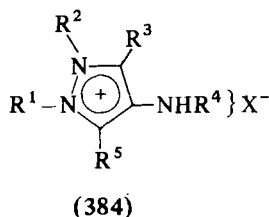
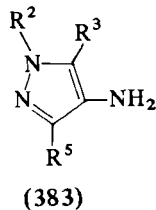
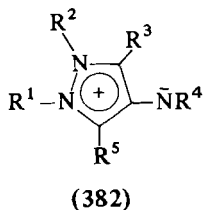
²²⁸ M. J. Nye and W.-P. Tang, *Tetrahedron* **28**, 463 (1972).

²²⁹ D. E. Metzler and E. E. Snell, *J. Amer. Chem. Soc.* **77**, 2431 (1955).

²³⁰ M. J. Nye, M. J. O'Hare, and W.-P. Tang, *J. Chem. Soc., Chem. Commun.*, 402 (1973).

2. 1,2-Diazol-4-imines (Anhydro-4-amino-1,2-diazolium Hydroxides) (382)

Meso-ionic 1,2-diazol-4-imines (382) have been recently obtained²²² as their *N*-mesyl ($R^4 = \text{MeSO}_2$) and *N*-tosyl ($R^4 = p\text{-MeC}_6\text{H}_4\text{SO}_2$) derivatives. Mesylation of 4-amino-1,3,5-trimethylpyrazole (383, $R^2 = R^3 = R^5 = \text{Me}$) followed by (i) methylation with methyl fluorosulfonate and (ii) treatment with perchloric acid gave the salt 384, $R^1 = R^2 = R^3 = R^5 = \text{Me}$, $R^4 = \text{MeSO}_2$, $X = \text{ClO}_4$. Deprotonation of this salt with aqueous alkali gave the compound 382, $R^1 = R^2 = R^3 = R^5 = \text{Me}$, $R^4 = \text{MeSO}_2$. The meso-ionic 1,2-diazol-4-imines 382, $R^1 = R^2 = R^3 = R^5 = \text{Me}$, $R^4 = p\text{-Me.C}_6\text{H}_4\text{SO}_2$, and 382, $R^1 = R^2 = \text{Me}$, $R^3 = R^5 = \text{Ph}$, $R^4 = p\text{-Me.C}_6\text{H}_4\text{SO}_2$, were similarly prepared.



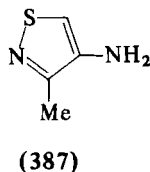
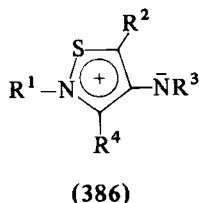
Thermal isomerization ($382 \rightarrow 385$, $R^1 = \text{Me}$ and $R^4 = \text{MeSO}_2$ or $p\text{-Me.C}_6\text{H}_4\text{SO}_2$) has been observed on heating in benzonitrile.²²² A related reaction occurs when the meso-ionic 1,2-diazol-4-imines (382, $R^1 = \text{Me}$, $R^4 = \text{MeSO}_2$ or $p\text{-Me.C}_6\text{H}_4\text{SO}_2$) are heated with dimethyl acetylenedicarboxylate in acetonitrile. This yields the products 385, $R^1 = \text{C}(\text{CO}_2\text{Me})=\text{CH}(\text{CO}_2\text{Me})$, $R^4 = \text{MeSO}_2$ or $p\text{-Me.C}_6\text{H}_4\text{SO}_2$.²²²

C. THIAZOLES

1,2-Thiazol-4-imines (Anhydro-4-amino-1,2-thiazolium Hydroxides) (386)

The pale yellow meso-ionic 1,2-thiazol-4-imine (386, $R^1 = R^4 = \text{Me}$, $R^2 = \text{H}$, $R^3 = p\text{-Me.C}_6\text{H}_4\text{SO}_2$) has been prepared from 4-amino-3-

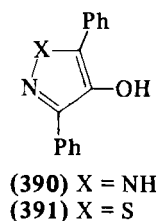
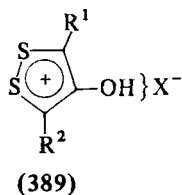
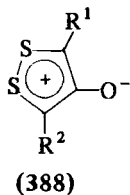
methylisothiazole (387) by a sequence similar to that used for meso-ionic 1,2-diazol-4-imines (382, $R^4 = p\text{-Me.C}_6\text{H}_4\text{SO}_2$).²²²



D. DITHIOLES

1,2-Dithiol-4-ones (Anhydro-4-hydroxy-1,2-dithiolium Hydroxides) (388)

The synthesis and some reactions of meso-ionic 1,2-dithiol-4-ones (388) have been recently reported. The brown compound 388, $R^1 = R^2 = \text{Ph}$, has been prepared by several methods: (i) the reaction between 1,1,3,3-tetrabromo-1,3-diphenylacetone ($\text{PhCBr}_2\text{COCBr}_2\text{Ph}$) and potassium ethyl xanthate,²⁴ (ii) the reaction between 1,3-diphenylpropanetrione hydrate and tetraphosphorus decasulfide,²⁴ (iii) 1,3-diphenylpropanetrione with hydrogen sulfide–hydrogen chloride in ethanol–chloroform yields the salt 389, $R^1 = R^2 = \text{Ph}$, $X = \text{Cl}$, which gives the meso-ionic 1,2-dithiol-4-one with triethylamine, pyridine, or aqueous sodium bicarbonate.^{23,231}



The diphenyl derivative 388, $R^1 = R^2 = \text{Ph}$, has an absorption band at 1495 cm^{-1} , which has been assigned to the carbonyl group.²⁴ This assignment could be questioned. The following chemical reactions of the compound 388, $R^1 = R^2 = \text{Ph}$, may be noted: (a) Raney nickel desulfurization followed by oxidation with manganese dioxide yields dibenzyl ketone,²⁴ (b) hydrazine yields 3,5-diphenyl-4-hydroxypyrazole (390),²⁴ (c) phenylhydrazine yields $\text{PhCH}_2\text{COCPh}=\text{NNHPh}$,²⁴ (d)

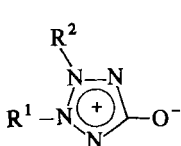
²³¹ A. Chinone, K. Inouye, and M. Ohta, *Bull. Chem. Soc. Jap.* **45**, 213 (1972).

heating at 275° yields sulfur and tetraphenyl-*p*-benzoquinone,²⁴ (e) methanolic ammonia yields 3,5-diphenyl-4-hydroxyisothiazole (391).²³ Reaction with aniline yields a blue compound, $C_{21}H_{13}SN$, which has been formulated as 3,4,5-triphenylisothiazole.²³ This assumption requires further study.

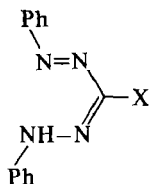
E. TETRAZOLES

1. 1,2,3,4-Tetrazol-5-ones (Anhydro-5-hydroxy-1,2,3,4-tetrazolium Hydroxides) (392)

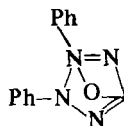
Meso-ionic 1,2,3,4-tetrazol-5-ones (392) have been known for many years, although they were not initially recognized as having betaine-type structures. Treatment of 1,5-diphenyl-3-nitroformazan (393, $X = NO_2$)



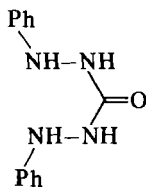
(392)



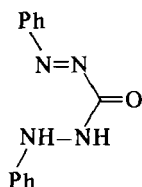
(393)



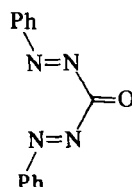
(394)



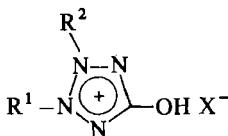
(395)



(396)



(397)



(398)

with acetic acid²³²⁻²³⁴ or isoamyl nitrite²³⁵ yields a white crystalline compound, $C_{13}H_{10}N_4O$, which was initially formulated with the bicyclic structure 394 by Bamberger.²³²⁻²³⁵ The same compound, $C_{13}H_{10}N_4O$,

²³² E. Bamberger, *Genfer Arch. Sci. Phys. Nat.* **6**, 384 (1898).

²³³ E. Bamberger, *Chem. Zentralbl.* **2**, 1050 (1898).

²³⁴ E. Bamberger, *Ber.* **44**, 3743 (1911).

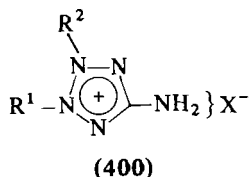
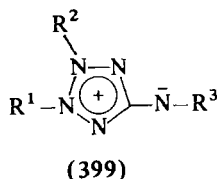
²³⁵ E. Bamberger, R. Padova, and E. Ormerod, *Ann.* **446**, 260 (1926).

was also obtained by the oxidation of diphenyl carbazide (**395**)^{235,236} or diphenylcarbazone (**396**)²³⁶ by Cazeneuve, who formulated the compound as having the acyclic structure **397**.²³⁶ Other 2,3-diaryl-1,2,3,4-tetrazol-5-ones (**392**) have been prepared by oxidation with amyl nitrite and hydrogen chloride of 1,5-diaryl-3-chloroformazans (**393**, X = Cl)²³⁷ or 1,5-diaryl-3-nitroformazans (**393**, X = NO₂).^{238,239}

Clearly the bicyclic structure **394** is unacceptable for the compound C₁₃H₁₀N₄O, and its ultraviolet spectrum is regarded^{142,240,241} as supporting the meso-ionic formulation **392** and excluding the bisphenylazo structure **397**. The 2,3-diphenyl derivative (**392**, R¹ = R² = Ph) forms salts²³⁵ (**398**, R¹ = R² = Ph) including a hydrochloride, hydriodide, chloroplatinate, perchlorate, and picrate; it is reduced to diphenylcarbazine (**395**) by ammonium sulfide.²³⁵

2. 1,2,3,4-Tetrazol-5-imines (Anhydro-5-amino-1,2,3,4-tetrazolium Hydroxides) (**399**)

Bamberger, Padova, and Ormerod reported in 1926²³⁵ an interesting but incomplete study of several unusual products obtained from 5-amino-2,3-diaryl-1,2,3,4-tetrazolium salts (**400**). Recently this topic has been the subject of a detailed study by I. S. Smith,²⁴² and the existence of several derivatives of meso-ionic 1,2,3,4-tetrazol-5-imines (**399**) has now been firmly established.²⁴² Comparison of Smith's recent results²⁴² with the earlier results of Bamberger *et al.*²³⁵ is instructive.



The molecular formulas and the structures originally proposed by Bamberger²³⁵ for a number of transformation products of 5-amino-2,3-diphenyl-1,2,3,4-tetrazolium chloride (**401**) are given in Fig. 8. The

²³⁶ P. Cazeneuve, *Bull. Soc. Chim. Fr.* **25**, 315 (1901).

²³⁷ M. O. Lozinskii and P. S. Pel'kis, *J. Gen. Chem. USSR* **33**, 106 (1963) [*CA* **59**, 612g (1963)].

²³⁸ R. G. Dubenko and P. S. Pel'kis, *J. Gen. Chem. USSR* **29**, 200 (1959) [*CA* **53**, 21906f (1959)].

²³⁹ L. S. Pupko, A. I. Dychenko, and P. S. Pel'kis, *Ukr. Khim. Zh.* **31**, 1306 (1965) [*CA* **64**, 12661f (1966)].

²⁴⁰ P. Grammaticakis, *C. R. Acad. Sci.* **234**, 528 (1952).

²⁴¹ P. B. Talukdar, S. K. Sengupta, A. K. Datta, and A. Chakravorty, *Indian J. Chem.* **11**, 611 (1973).

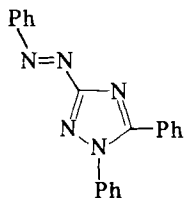
²⁴² I. S. Smith, M.Sc. Thesis, University of Sheffield (1972).

methods used to obtain these products from the salt **401** may be summarized as follows. Schotten-Baumann benzylation gave a yellow crystalline product, m.p. 232° (**402**), which was reduced by ammonium sulfide in ethanol giving a colorless product, m.p. 222° – 223° (**403**). Nitrosation of the salt **401** gave a yellow product, m.p. 176° – 177° (**404**), which yielded an orange isomer, m.p. 154° – 155° (**405**), on heating in ethanol.

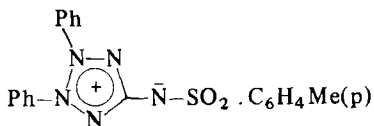
Repetition of the reactions summarized in Fig. 8 produced the results given in Fig. 9. There is a satisfying agreement between the old and new results, with one important exception: the molecular formula $C_{20}H_{15}N_3O$, originally assigned to the benzylation product (**402**), has had to be replaced by the molecular formula $C_{20}H_{17}N_3O$. Its formulation as 3-benzamido-1,5-diphenylformazan (**406**) is firmly established²⁴² by (i) its acid hydrolysis, yielding 3-amino-1,5-diphenylformazan (**393**, $X = NH_2$) and benzoic acid, and (ii) its dehydration, yielding 1,5-diphenyl-3-phenylazo-1,2,4-triazole (**410**) by boiling its solution in xylene. This triazole (**410**) is also formed by manganese dioxide oxidation of the hydrazo compound **407**.²⁴²

The transformation **401** \rightarrow **406** by Schotten-Baumann benzylation is a mysterious reaction, the mechanism of which is not obvious. Clearly a change in oxidation level has occurred, but related changes are known, and this is an incompletely understood aspect of the chemistry²⁴³ of formazans (**393**) and the corresponding tetrazolium cations. In contrast, the reaction of the salt with *p*-toluenesulphonyl chloride yields the meso-ionic 1,2,3,4-tetrazol-5-imine (**411**) directly.

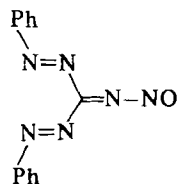
The thermal transformation **408** \rightarrow **409** presumably involves the valence tautomer **412** as an intermediate.²⁴² As a class, the type B meso-ionic 1,2,3,4-tetrazol-5-imines are exemplified by the *N*-nitroso and *N*-p-tosyl derivatives **408** and **411**. However, our current understanding²⁴² of



(410)



(411)



(412)

the results first reported in 1926 is a clear encouragement for the synthesis and examination of other classes of type B meso-ionic heterocycles.

²⁴³ A. W. Nineham, *Chem. Rev.* **55**, 355 (1955); N. D. Cheronis and H. Stein, *J. Chem. Educ.* **33**, 120 (1956); W. D. Hooper *Rev. Pure Appl. Chem.* **19**, 221 (1969); M. Laćan, I. Tabaković, and Ž. Čeković, *Tetrahedron* **30**, 2911 (1974).

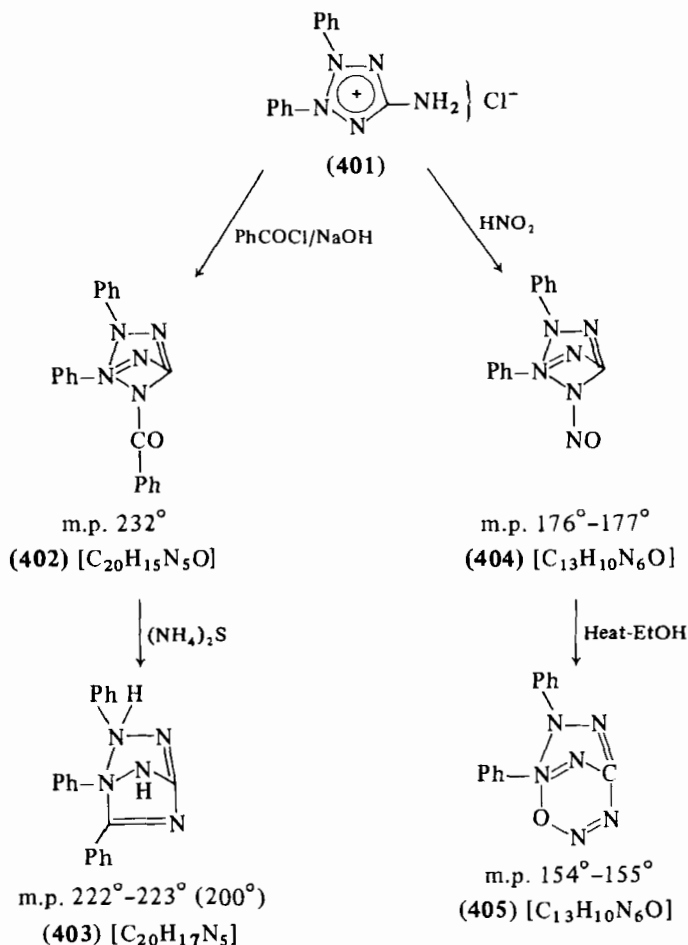
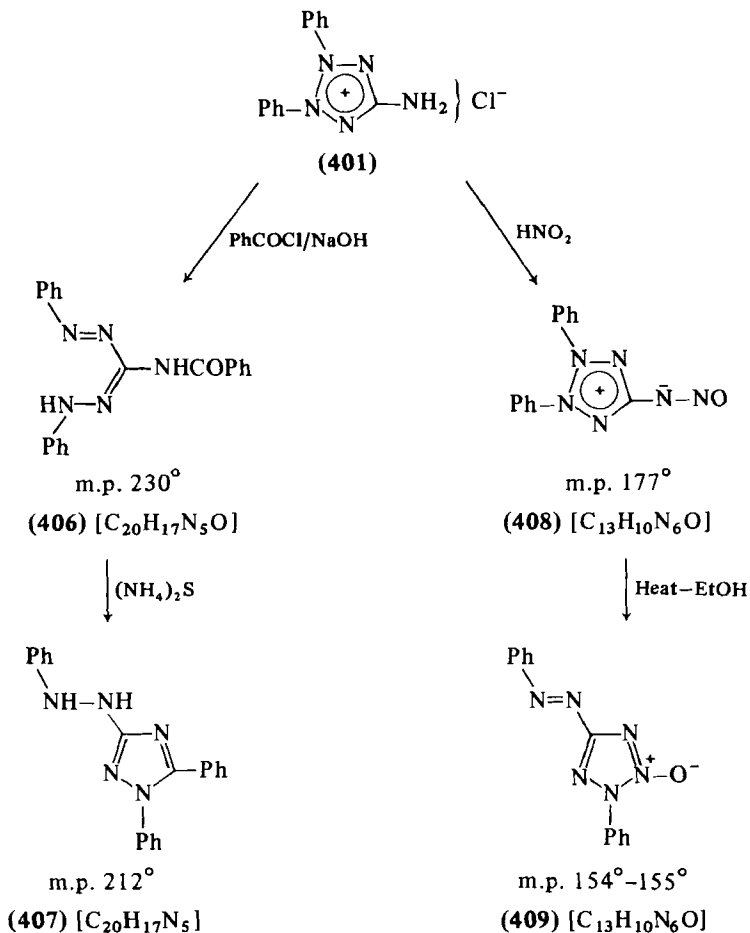


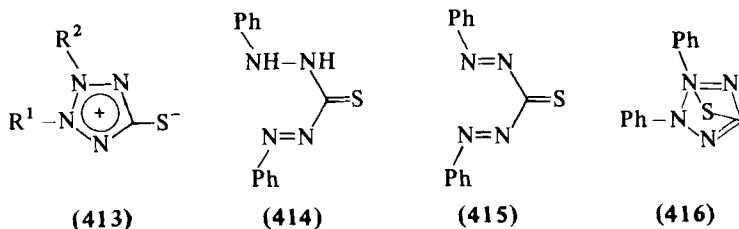
FIG. 8. A summary of the results and structural proposals given by Bamberger, Padova, and Ormerod.²³⁵

3. 1,2,3,4-Tetrazole-5-thiones (Anhydro-5-mercapto-1,2,3,4-tetrazolium Hydroxides) (413)

The *last* part of this section is devoted to the *first* meso-ionic heterocycle to be synthesized. It is called dehydrodithizone, and it is the most widely investigated representative of meso-ionic 1,2,3,4-tetrazole-5-thiones (413). Dehydrodithizone was first obtained by Emil Fischer in 1882²⁵ and his collaborator in this investigation was E. Besthorn, who subsequently discovered another meso-ionic compound, Besthorn's Red (93a).

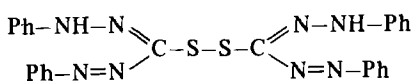
FIG. 9. A reinterpretation²⁴² of the results summarized in Fig. 8.

Dithizone (**414**) is a well-known reagent for the gravimetric estimation of heavy metal cations. Its oxidation with either manganese dioxide²⁵ or isoamyl nitrite²³⁵ yields an orange crystalline derivative called dehydrodithizone. This was initially formulated by Besthorn and

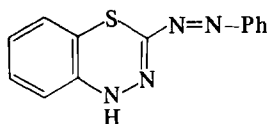


Fischer²³ as a bisphenylazo compound (415), whereas Bamberger *et al.* advocated²³⁵ the equivalent (416) of a betaine structure. A cyclic betaine structure was later supported^{142b,240,241} on the basis of its spectroscopic properties. Cogent arguments for the representation of dehydrodithizone as a meso-ionic heterocycle (413, $R^1 = R^2 = \text{Ph}$) were presented by Ogilvie and Corwin²⁴⁴ on the basis of its general chemistry and particular properties as a nucleophilic reagent.²⁴⁵ An X-ray crystallographic study²⁴⁶ of dehydrodithizone (413, $R^1 = R^2 = \text{Ph}$) confirmed its symmetrical structure and the planarity of its five-membered ring. The interatomic distances were in accord with an aromatic meso-ionic structure.

Oxidation of dithizone (414) with selenium dioxide or iodine in water gives the disulfide (417) which then disproportionates²⁶ on standing, yielding dithizone (414) and dehydrodithizone (413, $R^1 = R^2 = \text{Ph}$). This is closely analogous to the disproportionation $254 \rightarrow 251 + 253$.



(417)



(418)

The purple compound produced^{244,247,248} by the acid-catalyzed isomerization of dehydrodithizone (413, $R^1 = R^2 = \text{Ph}$) has been shown by an X-ray diffraction study²⁴⁹ to have the constitution 418.

The formation of various 1 : 1 adducts from dehydrodithizone 413, $R^1 = R^2 = \text{Ph}$, and various "1,3-dipolarophiles" has been reported.²⁵⁰ Thus, dimethyl acetylenedicarboxylate yields 419, $X = \text{COOMe}$, tetracyanoethylene yields 420, and ethoxycarbonylmethylenetriphenylphosphorane yields the betaine 421. These transformations have been considered as 1,3-dipolar cycloaddition reactions of a novel type. It seems to us rather unlikely that these transformations are *concerted* 1,3-dipolar cycloadditions: the alternative that they are reactions involving dipolar intermediates (e.g., 422, 423, and 424) should also be considered. The

²⁴⁴ J. W. Ogilvie and A. H. Corwin, *J. Amer. Chem. Soc.* **83**, 5023 (1961).

²⁴⁵ J. Ogilvie, V. K. Miyamoto, and T. C. Bruice, *J. Amer. Chem. Soc.* **83**, 2493 (1961).

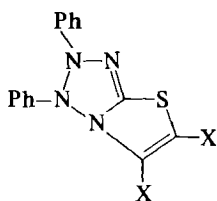
²⁴⁶ Y. Kushi and Q. Fernando, *Chem. Commun.*, 1240 (1969); *J. Amer. Chem. Soc.* **92**, 1965 (1970).

²⁴⁷ H. M. N. H. Irving and U. S. Mahnot, *Talanta* **15**, 811 (1968).

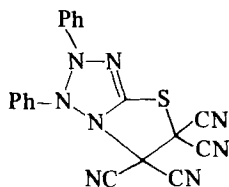
²⁴⁸ C. H. Carlin and A. H. Corwin, *Abstr. 157th Nat. Meeting, Amer. Chem. Soc., Minneapolis, ORGN 123* (1969).

²⁴⁹ W. S. McDonald, H. M. N. H. Irving, G. Raper, and D. C. Rupainwar, *Chem. Commun.*, 392 (1969).

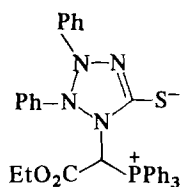
²⁵⁰ P. Rajagopalan and P. Penev, *Chem. Commun.*, 490 (1971).



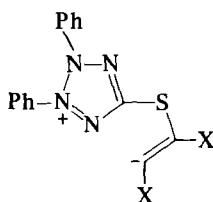
(419)



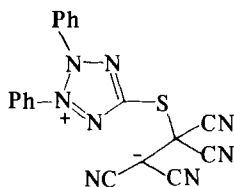
(420)



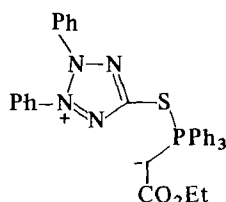
(421)



(422)

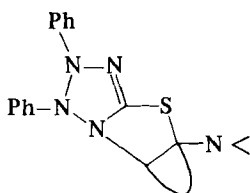


(423)

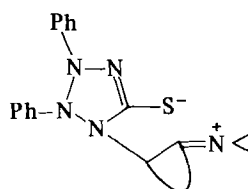


(424)

strong nucleophilic character of dithizone²⁴⁵ could assist in the generation of such dipolar intermediates (422, 423, and 424), and there is plenty of general analogy for such intermediates.²⁵¹ Particular reference may be made to the closely related cycloaddition reactions of meso-ionic 1,2-diazoles 373 and 382.²²² The transformation 424 → 421 could well involve a pentacovalent phosphorane intermediate as well.



(425)



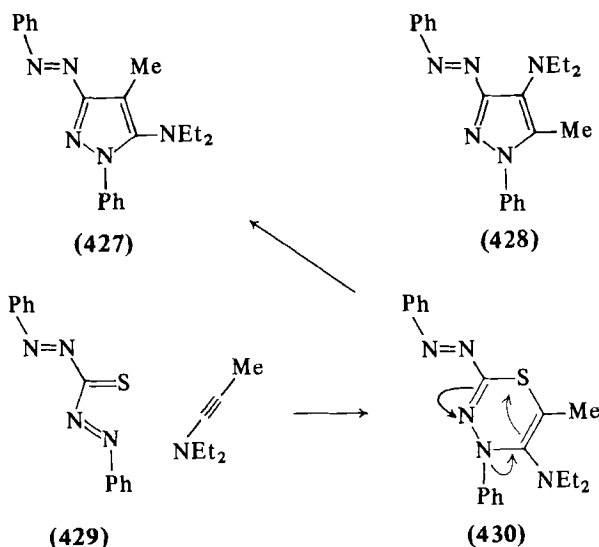
(426)

The reaction between enamines²⁵⁰ and dehydrodithizone 413, $R^1 = R^2 = \text{Ph}$, may well involve a different type of dipolar intermediate (426) whose formation matches the general characteristics of enamine reactions.

The reaction between dehydrodithizone 413, $R^1 = R^2 = \text{Ph}$, and ynamines has been recently reported.²⁵² Thus, with diethylaminoprop-1-yne the two products 427 and 428 are obtained. Their formation involves

²⁵¹ R. Gompper, *Angew. Chem., Int. Ed. Engl.* **8**, 312 (1969); "Cyclo-addition Reactions" (R. Gompper, ed.). Butterworths, London, 1972; C. K. Bradsher, *Advan. Heterocycl. Chem.* **16**, 289 (1974).

²⁵² G. V. Boyd, T. Norris, and P. F. Lindley, *J. Chem. Soc., Chem. Commun.*, 639 (1974).



extrusion of sulfur and one mechanistic possibility which has been considered is that a cycloaddition (429) takes place between the valence tautomer of dithizone and the ynamine. This could lead to the intermediate 430, which after cyclization (430; arrows) leads to an azomethine imine, which by extrusion of sulfur could yield the product 427. The initial cycloaddition (429) in the alternative sense could lead to the other product (428).

XI. The Physical Study and Theoretical Treatment of Meso-ionic Compounds

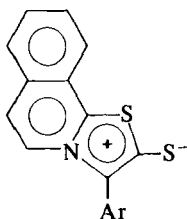
A. PHYSICAL METHODS

The spectroscopic properties of meso-ionic compounds have been discussed in detail elsewhere^{4,7,9b} and the reviewers do not feel that it would be useful to include a comprehensive account here. Ultraviolet, infrared, and nuclear magnetic resonance spectra of meso-ionic heterocycles provide general support for the conjugative interaction that would be expected for aromatic heterocycles,^{9b} but detailed interpretation of their spectra is not justifiable. Mass spectrometry has been shown to be particularly useful for distinguishing between pairs of meso-ionic isomers

(Section VIII),²⁰¹ and several accounts of the mass spectral fragmentation patterns of meso-ionic compounds have been published.^{201,253-258} Measurement of electric dipole moments encouraged the assignment of the original meso-ionic structures to the sydnone.²⁵⁹⁻²⁶⁴ More recently, electric dipole moment studies have given powerful support to the formulation of several new classes of heterocycle as meso-ionic compounds.^{19a,108,113}

B. X-RAY CRYSTALLOGRAPHY

a. *1,3-Thiazole-5-thiones* (109) (Section VII, C, 3). The crystal structure of the 2-*p*-bromophenyl derivative (431, Ar = *p*-Br.C₆H₄) has been reported and is consistent with the meso-ionic formulation of the molecule.^{72a}



(431)

b. *1,3-Thiazol-4-ones* (114) (Section VII, C, 4). The structure of the meso-ionic 1,3-thiazol-4-one (432) has been examined, and the observed bond lengths are consistent with a structure resembling the betaine

²⁵³ J. H. Bowie, R. A. Eade, and J. C. Earl, *Aust. J. Chem.* **21**, 1665 (1968).

²⁵⁴ R. S. Goudie, P. N. Preston, and M. H. Palmer, *Org. Mass Spectrom.* **2**, 953 (1969).

²⁵⁵ T. Shima, A. Ouchida, and Y. Asahi, *Shitsuryo Bunseki* **17**, 661 (1969) [*CA* **73**, 87149j (1970)].

²⁵⁶ R. C. Dougherty, R. L. Foltz, and L. B. Kier, *Tetrahedron* **26**, 1989 (1970).

²⁵⁷ W. K. Anderson and A. E. Friedman, *Org. Mass Spectrom.* **6**, 797 (1972).

²⁵⁸ K. T. Potts, R. Armbruster, E. Houghton, and J. Kane, *Org. Mass Spectrom.* **7**, 203 (1973).

²⁵⁹ W. Baker, W. D. Ollis, V. D. Poole, J. A. Barltrop, R. A. W. Hill, and L. E. Sutton, *Nature (London)* **160**, 366 (1947).

²⁶⁰ J. C. Earl, E. M. W. Leake, and R. J. W. Le Fèvre, *Nature (London)* **160**, 366 (1947).

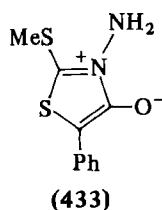
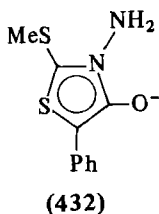
²⁶¹ J. C. Earl, E. M. W. Leake, and R. J. W. Le Fèvre, *J. Chem. Soc.*, 2269 (1948).

²⁶² R. A. W. Hill and L. E. Sutton, *J. Chim. Phys.* **46**, 244 (1949).

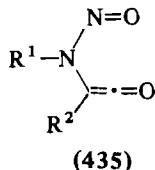
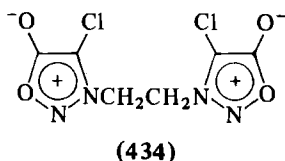
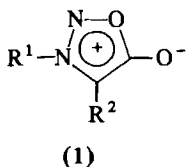
²⁶³ R. A. W. Hill and L. E. Sutton, *J. Chem. Soc.*, 746 (1949); 1482 (1953).

²⁶⁴ Y. G. Borod'ko and Y. K. Syrkin, *Dokl. Akad. Nauk SSSR* **134**, 1127 (1960) [*CA* **55**, 12039h (1961)].

433.^{78a} Thus, the CC distance (1.31 Å) corresponds to a double bond; the CS distances (1.81 and 1.77 Å) are comparatively long (cf. 1.72 Å in thiophene), and the CO bond length (1.33 Å), which is rather longer than that observed for sydnones (1.2 Å), suggests a structure in which a substantial negative charge is associated with the oxygen atom.



c. *1,2,3-Oxadiazol-5-ones* (Sydnones) (1). The crystal structures of two sydnones have been determined. A study²⁶⁵ of *N-p*-bromophenyl sydnone (1, $R^1 = p\text{-Br} \cdot \text{C}_6\text{H}_4$, $R^2 = \text{H}$) showed that (i) the meso-ionic ring is planar; (ii) the exocyclic CO distance (1.20 Å) is essentially that of a double bond; (iii) the ring CO distance (1.42 Å) is close to that expected for a CO single bond; (iv) the *p*-bromophenyl ring is inclined at a dihedral angle of 27.6° to the plane of the sydnone ring. Because the crystal geometry of the sydnone 1, $R^1 = p\text{-Br} \cdot \text{C}_6\text{H}_4$, $R^2 = \text{H}$, may be influenced by a "charge transfer" interaction between the carbonyl oxygen atom and a neighboring bromine atom, the structure of 4,4'-dichloro-3,3'-ethylene bis-sydnone (434) has also been determined:²⁶⁶ the structure of this sydnone (434) is essentially the same as that observed by the previous workers.



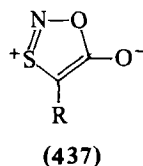
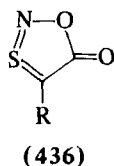
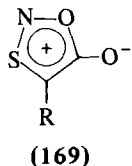
The sydnone ring geometries obtained in these two studies are not in obvious agreement with the suggestion that the sydnone ring is aromatic. In particular, the ring CO distance is longer than expected while the exocyclic CO distance is shorter than would be expected for an oxygen atom associated with a large negative charge. These observations, together with the rather large $\text{CCO}_{\text{exocyc}}$ bond angles (135.7° and 135.5°) have led to the suggestion²⁶⁶ that the valence tautomeric ketene

²⁶⁵ H. Bärnighausen, F. Jellinek, J. Munnik, and A. Vos, *Acta Crystallogr.* **16**, 471 (1963).

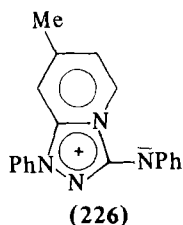
²⁶⁶ W. E. Thiessen and H. Hope, *J. Amer. Chem. Soc.* **89**, 5977 (1967).

435 makes a substantial contribution as a canonical form to the meso-meric sydnone structure (1).

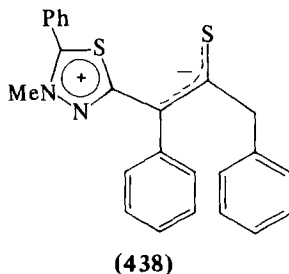
d. *1,3,2-Oxathiazol-5-ones* (**169**) (Section VII, F, 1). The crystal structure of 4-phenyl-1,3,2-oxathiazol-5-one (**169**, R = Ph) has been reported.¹¹⁷ The ring is apparently not planar; the carbonyl carbon atom is out of the plane of the other four ring atoms by 0.026 Å. The dihedral angle between the two rings is 16.6°. The observed bond distances (CO, 1.195 and 1.405 Å; CC, 1.443 Å; CS, 1.659 Å; NO, 1.375 Å; SN, 1.604 Å) support the structure with tetravalent sulfur (**436**), but this may alternatively be interpreted as indicating that the betaine tautomer (**437**) makes an important contribution to the structure. The C=O bond length (1.195 Å)¹¹⁷ is almost identical with that observed for sydnones (1.20 Å).^{265,266}



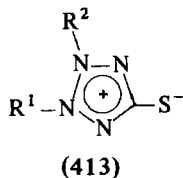
e. *1,2,4-Triazol-3-imines* (**216**) (Section VII, G, 5). A preliminary account of an X-ray crystallographic study of the 1,2,4-triazol-3-imine (**226**) has been reported.¹⁴⁷



f. *1,3,4-Thiadiazol-2-enes* (**261**) (Section VII, H, 4). A detailed structural determination of the 1,3,4-thiadiazol-2-ene (**438**) has been reported.¹⁷⁵ The separation of the two sulfur atoms (2.79 Å) indicates some interaction.

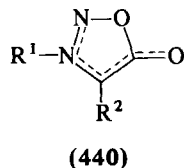
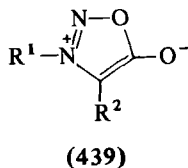
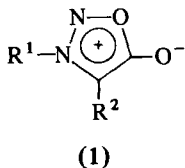


g. *1,2,3,4-Tetrazole-5-thiones* (413) (Section X, E, 3). A detailed investigation of the crystal structure of dehydrodithizone (413, $R^1 = R^2 = \text{Ph}$) has been reported²⁴⁶ and is of particular interest in that it is the only known crystal structure of a type B meso-ionic heterocycle. The five-membered ring and the sulfur atom are coplanar, and all the bond lengths (NN, 1.313 and 1.318 Å; CN, 1.360 Å; CS, 1.687 Å) are intermediate between single and double bond lengths. These features are all entirely consistent with the meso-ionic structure 413.



C. ESCA SPECTROSCOPY

a. *1,2,3-Oxadiazol-5-ones* (Sydnones) (1). The ESCA spectra of *N*-phenylsydnone (1, $R^1 = \text{Ph}$, $R^2 = \text{H}$)^{172,267} and *N*-methylsydnone (1, $R^1 = \text{Me}$, $R^2 = \text{H}$)²⁶⁷ have been recorded. The core electron binding energies of the two nitrogen atoms in the sydnone ring (Table III) differ by 1.4–2.0 eV, suggesting that there is a considerable difference in the formal charges associated with these two nitrogen atoms. Similarly, the molecular environment of the two oxygen atoms in the sydnone nucleus are quite different. For *N*-methylsydnone (1, $R^1 = \text{Me}$, $R^2 = \text{H}$), the intramolecular chemical shifts of the core electron binding energies of the carbon, nitrogen, and oxygen atoms have been estimated using *ab initio* calculations and applying Koopmans' theorem.²⁶⁷ The results are in good agreement with experiment, although the absolute values of the core ionization potentials (Table III) are calculated to be high (probably owing to the neglect of orbital relaxation on ionization). Attempts to correlate the observed core ionization potentials with formal charges calculated by *ab initio* and semiempirical intermediate neglect of differential overlap (INDO) methods were less successful.²⁶⁷



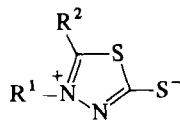
²⁶⁷ M. Barber, S. J. Broadbent, J. A. Connor, M. F. Guest, I. H. Hillier, and H. J. Puxley, *J. Chem. Soc., Perkin Trans. II*, 1517 (1972); L. J. Aarons, M. F. Guest, and I. H. Hillier, *J. Chem. Soc., Faraday Trans. II* **68**, 1866 (1972).

On the basis of their ESCA spectra, two interpretations of the best representation of the bonding in sydnones have been proposed. Patsch and Thieme¹⁷² concluded that the differences in the binding energies for the two nitrogen atoms and the two oxygen atoms support a betaine structure (439). Alternatively, Hillier and his co-workers,²⁶⁷ who based their conclusion on both spectroscopic evidence and calculations, suggested that the structure 440 best represents 3-alkylsydnones. These two representations, 439 and 440, are in fact very similar; an important common feature is the nonconjugation of the ring oxygen atom in the cyclic π -electron system.

b. *1,2,4-Triazole-3-thiones* (227). ESCA spectra of two meso-ionic 1,2,4-triazole-3-thiones (227) (Table III) have been measured.^{149b} The results which support the meso-ionic formulation 227, are quite distinct from those obtained for derivatives of the isomeric meso-ionic 1,3,4-thiadiazol-2-imine system (247).

c. *1,3,4-Thiadiazol-2-imines* (247). Representatives of the meso-ionic 1,3,4-thiadiazol-2-imines (247) have only recently been prepared (Section VII, H, 2), although the isomeric meso-ionic 1,2,4-triazole-3-thiones (227) have been known for a number of years (Section VII, G, 6). ESCA spectra of eight derivatives of the 1,3,4-thiadiazol-2-imines (247) have been reported (Table III).^{149b} These spectra are quite distinct from those of the 1,2,4-triazole-3-thiones (227) and provide further support for the formulation of these compounds as 1,3,4-thiadiazol-2-imines (247). In particular, the sulfur atom in the ring position has a core binding energy (ca. 163.5 eV) (Table III) quite distinct from that of the exocyclic sulfur atom (ca. 160.5 eV) in the meso-ionic 1,2,4-triazole-3-thiones (227) (Table III).

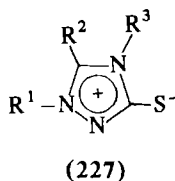
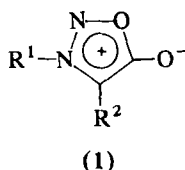
d. *1,3,4-Thiadiazole-2-thiones* (251). The ESCA spectra of two meso-ionic 1,3,4-thiadiazole-2-thiones (251) (Table III) have been recorded.¹⁷² The difference in the core binding energy of the two nitrogen atoms (ca. 2.3 eV) and the difference between the two sulfur atoms (ca. 2.5 eV) support a betaine structure (441) in which similar atoms are associated with quite different electron densities. The core binding energies of the two sulfur atoms have values (Table III) that correspond to those observed for the ring sulfur atom in the meso-ionic 1,3,4-thiadiazol-2-imines (247) and the exocyclic sulfur atom in the meso-ionic 1,2,4-triazole-3-thiones (227).



(441)

TABLE

ESCA SPECTRA OF



Compound	R ¹	R ²	R ³
Sydnone (1) ^{172,267}	Ph Me	H H	
1,2,4-Triazole-3-thiones (227) ^{149b}	Ph Ph	<i>m</i> -NO ₂ -C ₆ H ₄ <i>t</i> -C ₄ H ₉	Allyl Allyl
1,3,4-Thiadiazol-2-imines (247) ^{149b}	Me Me Me Me Me Me Me Me	Ph Ph Ph Ph Ph <i>p</i> -Cl.C ₆ H ₄ <i>p</i> -EtO.C ₆ H ₄	OEt NMe ₂ Me <i>t</i> -C ₄ H ₉ Ph <i>p</i> -NO ₂ -C ₆ H ₄ OEt OEt
1,3,4-Thiadiazole-2-thiones (251) ¹⁷²	Me Me	Ph <i>p</i> -Cl.C ₆ H ₄	

D. MOLECULAR ORBITAL CALCULATIONS

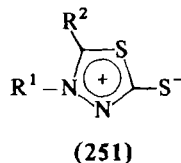
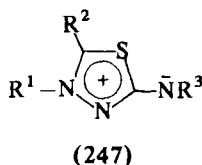
Ever since the discovery of the sydnones (1) and the introduction of the term meso-ionic,¹ the class of meso-ionic heterocycles has aroused much theoretical interest because of the problems associated with their representation. Most theoretical studies have been concerned with molecular orbital (MO) calculations on the sydnones, and increasingly sophisticated calculations have been reported with the development of improved computer facilities. A summary has been recently presented²⁶⁸ of the various types of MO calculations which are currently of interest to organic chemists.

a. *1,2,3-Oxadiazol-5-ones (Sydnones) (1)*. (i) *π-Electron calculations*. The first MO calculations carried out for the sydnone ring were Hückel

²⁶⁸ C. A. Ramsden, *Chem. Brit.* to be published (1976).

III

MESO-IONIC HETEROCYCLES



Core electron binding energies (eV)			
C(1s)	N(1s)	O(1s)	S(2p)
285.6; 287.9	399.4; 401.4; 400.8; 402.2	530.3; 532.7; 531.4; 533.8	
	401.2; 402.6		
	398.2; 399.9; 400.1; 405.0 (NO ₂) 397.8; 399.2; 400.2		160.6 160.4
	397.0; 398.2; 400.7		163.9
	397.0; 398.2; 398.9 (NMe ₂); 401.2		163.5
	396.6; 398.2; 400.5		163.3
	397.0; 398.2; 400.4		163.6
	396.6; 398.1; 400.1		163.2
	396.8; 398.3; 400.2; 404.6 (NO ₂)		163.7
	396.9; 398.2; 400.7		163.7
	397.1; 398.2; 400.6		163.7
	398.2; 400.6		161.1; 163.7
	398.3; 400.5		160.7; 163.2

calculations.²⁶⁹⁻²⁷² These results were in general agreement with the observed magnitude and direction of the electric dipole moment of the sydnone ring, although the calculated moments were far too large. The use of the ω -Hückel method gave more satisfactory calculated values for dipole moments.^{273,274} Later the Pariser-Parr-Pople (PPP) method and modifications of this method were applied to the sydnone ring and used to calculate charge distributions and electronic spectra

²⁶⁹ H. C. Longuet-Higgins, *J. Phys. Chim.* **46**, 246 (1949).

²⁷⁰ L. E. Orgel, T. L. Cottrell, W. Dick, and L. E. Sutton, *Trans. Faraday Soc.* **47**, 113 (1951).

²⁷¹ D. A. Bochvar and A. A. Bagatur'yants, *Zh. Fiz. Khim.* **39**, 1631 (1965); [*CA* **64**, 3329a (1966)].

²⁷² J. A. Singer and W. P. Purcell, *J. Med. Chem.* **10**, 754 (1967).

²⁷³ L. B. Kier and E. B. Roche, *J. Pharm. Sci.* **55**, 807 (1966).

²⁷⁴ E. B. Roche and L. B. Kier, *Tetrahedron* **24**, 1673 (1968).

with modest success.^{193,275-279} Since these π -electron methods involve quite serious approximations, particularly when applied to heterocyclic systems, and much more sophisticated and accurate methods are now available, these early calculations are only of historical interest, although they did play an important rôle in the development of the understanding of bonding in sydnones.

(ii) *All valence electron semiempirical calculations.* Several semiempirical MO calculations of sydnones (**1**) have now been reported. The earliest study was the application of the extended Hückel method (EH) to *N*-phenylsydnone (**1**, $R^1 = \text{Ph}$, $R^2 = \text{H}$).²⁸⁰ In this calculation the geometry of the molecule was assumed to be the same as that obtained for it in the X-ray study of *N*-*p*-bromophenylsydnone (**1**, $R^1 = p\text{-Br} \cdot \text{C}_6\text{H}_4$, $R^2 = \text{H}$) (Section XI, B). The calculated electric dipole moment was rather large (μ_{calc} 12.5 D; μ_{exp} 6.48 D). When the total energy of *N*-phenylsydnone (**1**, $R^1 = \text{Ph}$, $R^2 = \text{H}$) was calculated at several inter-ring torsion angles, an energy minimum was found when the angle was 27° , which is in remarkable agreement with the torsion angle of 27.6° observed for *N*-*p*-bromophenylsydnone (**1**, $R^1 = p\text{-Br} \cdot \text{C}_6\text{H}_4$, $R^2 = \text{H}$).²⁸⁰ More recently, the charge iterative extended Hückel method (IEH) has been applied to *N*-methylsydnone (**1**, $R^1 = \text{Me}$, $R^2 = \text{H}$).²⁸¹ Here the calculated dipole moments are in rather better agreement with experiment (μ_{calc} 7.04 D; μ_{exp} 7.31 D). A detailed discussion of the charge distribution has also been given.²⁸¹

Complete neglect of differential overlap (CNDO) calculations with inclusion of configuration interaction (CNDO CI) have been reported for the unsubstituted sydnone molecule (**1**, $R^1 = R^2 = \text{H}$) and *N*-methylsydnone (**1**, $R^1 = \text{Me}$, $R^2 = \text{H}$);²⁸² geometries were based on *N*-*p*-bromophenylsydnone (**1**, $R^1 = p\text{-Br} \cdot \text{C}_6\text{H}_4$, $R^2 = \text{H}$). The calculated dipole moment of *N*-methylsydnone (**1**, $R^1 = \text{Me}$, $R^2 = \text{H}$) is in very good agreement with experiment (μ_{calc} 7.57 D; μ_{exp} 7.31 D), but the calculated electronic spectrum is less satisfactory.²⁸² Similar results have been ob-

²⁷⁵ D. A. Bochvar and A. A. Bagatur'yants, *Zh. Fiz. Khim.* **39**, 1631 (1965) [CA **64**, 3329a (1966)].

²⁷⁶ D. A. Bochvar and A. A. Bagatur'yants, *Teor. Eksp. Khim.* **5**, 19 (1969) [CA **71**, 33577n (1969)].

²⁷⁷ E. V. Borisov, L. E. Kholodov, A. A. Bagatur'yants, and V. G. Yashunskii, *Khim. Geterotsikl. Soedin.* **7**, 1407 (1971) [CA **76**, 98939e (1972)].

²⁷⁸ D. A. Bochvar, A. A. Bagatur'yants, and E. V. Borisov, *Zh. Fiz. Khim.* **46**, 523 (1972) [CA **76**, 146892h (1972)].

²⁷⁹ J. Sauer and C. Jung, *Z. Chem.* **13**, 434 (1973).

²⁸⁰ L. B. Kier, *Tetrahedron Lett.*, 1233 (1967).

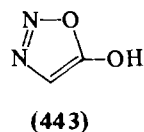
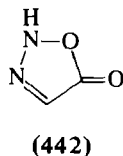
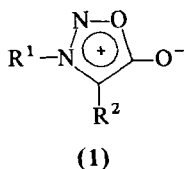
²⁸¹ O. Mårtensson, *J. Mol. Struct.* **9**, 321 (1971).

²⁸² G. H. Schmid, *J. Mol. Struct.* **5**, 236 (1970).

tained for CNDO/2 calculations on the unsubstituted sydnone (1, $R^1 = R^2 = H$) (μ_{calc} 6.82 D).²⁸³

INDO calculations for *N*-methylsydnone (1, $R^1 = \text{Me}$, $R^2 = H$) and *N*-phenylsydnone (1, $R^1 = \text{Ph}$, $R^2 = H$) have been reported;²⁶⁷ again the geometries were based on the X-ray study of *N*-*p*-bromophenylsydnone (1, $R^1 = p\text{-Br} \cdot \text{C}_6\text{H}_4$, $R^2 = H$). The calculated charge distribution in both these sydrones (1, $R^1 = \text{Me}$, and Ph , $R^2 = H$) is very similar, and this is consistent with the observation of very similar core binding energies in their ESCA spectra (Table III) (Section XI,C). The calculations of the charge distribution in *N*-methylsydnone by CNDO²⁸² and INDO²⁶⁷ calculations are very similar. The exocyclic oxygen atom is associated with a substantial negative charge (ca. 0.45 eu), and the adjacent carbon atom carries an almost equal positive charge. The nitrogen atom attached to the methyl group is positively charged (ca. 0.25 eu), and the adjacent carbon and nitrogen atoms carry rather smaller negative charges (ca. 0.1–0.2 eu).

(iii) *Ab initio* calculations. Two *ab initio* studies of *N*-methylsydnone (1, $R^1 = \text{Me}$, $R^2 = H$) have been reported; in each case the molecular geometry was based on that of 3,3'-ethylenebissydnone (434) (Section XI,B).^{267,284} By applying Koopmans' theorem, the calculations give intramolecular chemical shifts of the core electron binding energies that are in good agreement with the observed ESCA spectrum (Table III) (Section XI,C).²⁶⁷ The calculated dipole moment (μ_{calc} 5.98 and 6.28 D; μ_{exp} 7.31 D) and ionization potential (I_{calc} 8.75 eV; I_{exp} 8.9 eV) are in satisfactory agreement with experiment.



The charge distributions of the sydnone ring calculated by these *ab initio* methods^{267,284} show one significant difference from those given by CNDO and INDO calculations, namely a reversal of the positive and negative charges on the nitrogen atoms.

In addition, *ab initio* calculations for the unknown unsubstituted sydnone molecule (1, $R^1 = R^2 = H$) and the tautomeric species 2*H*-1,2,3-oxadiazol-5-one (442) and 5-hydroxy-1,2,3-oxadiazole (443) have been reported.²⁸⁴ The meso-ionic tautomer (1) is calculated to be less stable

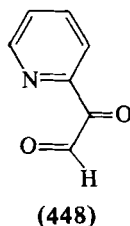
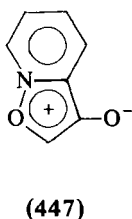
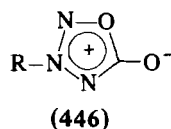
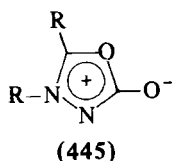
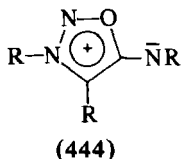
²⁸³ J. E. Bloor, B. R. Gilson, and F. P. Billingsley, II, *Theor. Chim. Acta* 12, 360 (1968).

²⁸⁴ M. H. Palmer, A. J. Gaskell, and M. S. Barber, *J. Mol. Struct.* 12, 197 (1972).

than the tautomers **442** and **443**. However, since total energy was not minimized with respect to geometry, these results are questionable.

b. *Other Meso-ionic Systems.* A number of π -electron MO calculations on systems other than the sydnones (**1**) have been reported:⁴ these include the 1,2,3-oxadiazol-5-imines (sydnone imines) (**444**),^{4,271,278} the 1,3,4-oxadiazol-2-ones (isosydnones) (**445**),¹⁹³ and the 1,2,3,4-oxatriazol-5-ones (**446**).¹⁹³ Since much more sophisticated MO methods are now available, the reviewers do not think that a detailed report of these early calculations is useful.

PPP calculations have been used to predict the properties of the type B meso-ionic 1,2-oxazol-4-one (**447**),²⁸⁵ although the possibility that the valence tautomer **448** may be more stable was not considered. So far, the three predictions that this as yet unknown compound (**447**) (i) "*should show two absorption maxima at about 460 and 440 m μ (approximation ± 30 m μ),*" (ii) "*should appear as an orange or red substance,*" and (iii) "*should be handled and kept at low temperatures*" have not been confirmed.²⁸⁵ We leave to the judgment of others the extent to which their confidence can and should be placed in these three predictions.



XII. Pharmacological Activity of Meso-ionic Compounds

The wide range of structural variation presented by meso-ionic heterocycles of type A and type B is such that some members have attracted the attention of medicinal chemists. Many different biological activities have been claimed, particularly in the patent literature. The authors of this review are not competent to provide a critical appraisal of the biological activities that have been attributed to meso-ionic compounds. These are therefore only briefly recorded in the following summary, and the original papers or patents should be consulted for details.

²⁸⁵ L. Paoloni and A. Ciampi, *J. Heterocycl. Chem.* **5**, 7 (1968).

For reasons given in the Introduction, the chemistry of sydnones and sydnone imines is not discussed in the chemistry section of the review. Examination of their pharmacological activity is, however, given in this section.

The possibility that meso-ionic compounds might have potential value as biologically active substances has been emphasized particularly in an excellent review by Kier and Roche.⁴ Kier has also put forward stimulating proposals concerning possible general applications of MO theory to drug research.²⁸⁶

a. *1,2,3-Oxadiazol-5-ones* (*Sydnones*) (1). The earliest reported consideration of sydnones (1) as biologically active compounds was made by Brookes and Walker in 1957.²⁸⁷ The relation between their meso-ionic structure (1) and the zwitterionic structure of amino acids suggested that sydnones might exhibit properties as natural amino acid antagonists. However, no antibacterial activity was observed.²⁸⁷ A wide range of biological properties has been claimed for various sydnone derivatives and these have been well reviewed up to 1966.^{4,288} Later references are included in this review.

The following activities have been claimed for sydnone derivatives (26): antibacterial,^{4,287-300} antitumor,⁴ antifungal,^{301,302} anti-

²⁸⁶ L. B. Kier, "Molecular Orbital Theory in Drug Research." Academic Press, New York, 1971.

²⁸⁷ P. Brookes and J. Walker, *J. Chem. Soc.*, 4409 (1957).

²⁸⁸ E. Ackermann, *Pharmazie* 22, 537 (1967) [CA 68, 28171j (1968)].

²⁸⁹ S. A. Zotova, E. N. Padeiskaya, V. G. Yashunskii, and G. N. Pershin, *Zh. Org. Khim.* 2, 728 (1966) [CA 63, 10657f (1966)].

²⁹⁰ T. Naito, S. Nakagawa, K. Takahashi, K. Masuko, K. Fujisawa, and H. Kawaguchi, *J. Antibiot. (Tokyo)* 21, 290 (1968) [CA 70, 28862b (1969)].

²⁹¹ T. Naito, S. Nakagawa, K. Takahashi, K. Fujisawa, and H. Kawaguchi, *J. Antibiot. (Tokyo)* 21, 300 (1968) [CA 70, 37698e (1969)].

²⁹² T. Takano (Fujisawa Pharmaceutical Co., Ltd.), *S. African* 68 02,695 [CA 71, 124458r (1969)].

²⁹³ G. Pala, G. Coppi, A. Mantegani, and E. Crescanzi, *Chim. Ther.* 4, 26 (1969) [CA 71, 3329r (1969)].

²⁹⁴ K. Hattori and S. Horibe, *Japan* 70 37,975 [CA 74, 100034k (1971)].

²⁹⁵ Fujisawa Pharm. Co., Ltd., *Brit* 1,187,323 [CA 73, 3923w (1970)].

²⁹⁶ (a) Fujisawa Pharm. Co., Ltd. *Japan* 71 02,341; 71 02,342; 71 02,343; 71 02,344 [CA 74, 141838u; 141837t; 141831m; 141832n (1971)]; (b) Fujisawa Pharm. Co., Ltd. *Japan* 71 02,340; 71 02,345; 71 02,346 [CA 75, 5924n; 5922k; 5921j (1971)].

²⁹⁷ Roussel-Uclaf., *BE* 757792-Q.

²⁹⁸ G. R. Forker and V. P. Francois (Beecham Group Ltd.), *S. African* 71 00,171 [CA 76, 140793e (1972)].

²⁹⁹ M. Kurita, Y. Saito, and T. Teraji (Fujisawa Chem. Co., Ltd.), *Japan* 71 24,037 [CA 75, 118330j (1971)].

³⁰⁰ T. Takano (Fujisawa Pharm. Co., Ltd.), *Japan* 71 21,715 [CA 76, 14557t (1972)].

³⁰¹ D. Davis, H. J. Becker, and E. F. Rogers, *Phytopathology* 49, 821 (1959).

³⁰² E. F. Roger and D. Davis (Merck and Co., Inc.), *U.S.* 3,189,520 [CA 63, 7605d (1965)].

malarial,³⁰³⁻³⁰⁶ antiparasitic,³⁰⁷ analgesic,³⁰⁸⁻³²⁵ anti-inflammatory,^{309-311,314-319,321-323} coccidiostatic,³²⁶ hypotensive,³²⁷ hypoglycemic,⁴ diuretic,⁴ hepatotoxic,³²⁸ and insecticidal.^{312,313,329,330} Central

³⁰³ W. H. Nyberg and C. C. Cheng, *J. Med. Chem.* **8**, 531 (1965).

³⁰⁴ S. G. Boots and C. C. Cheng, *J. Heterocycl. Chem.* **4**, 272 (1967).

³⁰⁵ I. C. Popoff and G. H. Singhal, *J. Med. Chem.* **11**, 631 (1968).

³⁰⁶ D. J. McCaustland, W. H. Burton, and C. C. Cheng, *J. Heterocycl. Chem.* **8**, 89 (1971).

³⁰⁷ G. Pala, A. Mantegani, G. Coppi, and R. Genova, *Chim. Ther.* **4**, 31 (1969) [CA **71**, 3328q (1969)].

³⁰⁸ Y. Imashiro and K. Masuda (Takeda Chem. Ind., Ltd.) Ger. Offen. 1,802,568 [CA **73**, 35379q (1970)].

³⁰⁹ Y. Saito and T. Kamitani (Takeda Chem. Ind., Ltd.), Japan. 70 10,509 [CA **73**, 14852y (1970)].

³¹⁰ Y. Saito and T. Kamitani (Takeda Chem. Ind., Ltd.), Japan. 70 10,510 [CA **73**, 14853z (1970)].

³¹¹ T. Kamitani, Y. Saito, and T. Teraji (Fujisawa Pharm. Co., Ltd), Japan. 70 17,188 [CA **73**, 66586j (1970)].

³¹² K. Masuda and T. Okutani (Takeda Chem. Ind., Ltd.), Japan. 70 20,902 [CA **73**, 87927m (1970)].

³¹³ K. Masuda and T. Okutani (Takeda Chem. Ind., Ltd.), Japan. 70 20,903 [CA **73**, 87928n (1970)].

³¹⁴ Y. Saito and T. Kamitani (Fujisawa Pharm. Co., Ltd.), Japan. 70 21,507 [CA **73**, 87923g (1970)].

³¹⁵ Y. Saito and T. Kamitani (Fujisawa Pharm. Co., Ltd.), Japan. 70 21,508 [CA **73**, 87924h (1970)].

³¹⁶ Y. Saito and T. Kamitani (Fujisawa Pharm. Co., Ltd.), Japan. 70 21,509 [CA **73**, 87925j (1970)].

³¹⁷ Y. Saito and T. Kamitani (Fujisawa Pharm. Co., Ltd.), Japan. 70 21,710 [CA **73**, 87926k (1970)].

³¹⁸ T. Kamitani, Y. Saito, and T. Teraji (Fujisawa Pharm. Co., Ltd.), Japan. 70 26,087 [CA **73**, 109786u (1970)].

³¹⁹ T. Kamitani and Y. Saito (Fujisawa Pharm. Co., Ltd.), Japan. 70 26,091 [CA **73**, 109787v (1970)].

³²⁰ T. Kamitani, Y. Saito, and T. Teraji (Fujisawa Pharm. Co., Ltd.), Japan. 70 26,092 [CA **74**, 3633x (1971)].

³²¹ T. Kamiya, Y. Saito, and T. Teraji (Fujisawa Pharm. Co., Ltd.), Japan. 72 32,072 [CA **78**, 4257x (1973)].

³²² T. Kamiya, Y. Saito, and T. Teraji (Fujisawa Pharm. Co., Ltd.), Japan. 72 32,073 [CA **78**, 4259z (1973)].

³²³ T. Kamitani, Y. Saito, and T. Terachi (Fujisawa Pharm. Co., Ltd.), Japan. 72 07,376 [CA **76**, 153748u (1972)].

³²⁴ Y. Imashiro and K. Masuda (Takeda Chem. Ind., Ltd.), U.S. 3,642,793 [CA **76**, 140838y (1972)].

³²⁵ Takeda Chem. Ind., Ltd., Fr. M. 7421 [CA **78**, 58430s (1973)].

³²⁶ P. M. Weintraub, C. O. Baughn, and R. E. Bambury (Richardson-Merrell Inc.), U.S. 3,574,856 [CA **75**, 67496h (1971)].

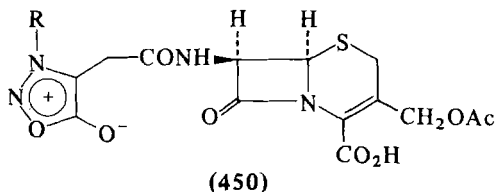
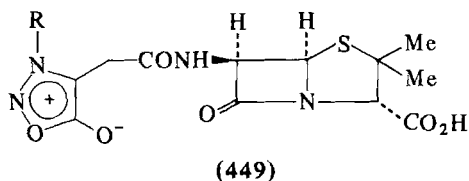
³²⁷ K. Masuda, K. Kikuchi, and Y. Imajo (Takeda Chem. Ind., Ltd.), Japan. 72 29,511 [CA **78**, 124597e (1973)].

³²⁸ P. Lange and F. Jung, *Acta Biol. Med. Ger.* **27**, 425 (1971) [CA **76**, 136508y (1972)].

³²⁹ Farbenfabriken Bayer Akt.-Ges., Brit. 823,001 [CA **54**, 8854b (1960)].

³³⁰ P. F. Wiley (Eli Lilly and Co.), U.S. 3,224,937 [CA **64**, 14194e (1966)].

nervous system activity—convulsant and anti-convulsant—have been claimed^{331–333} as well as the ability to function as inhibitors of monoamine oxidase³³⁴ and other biotransformations.^{335–337}



A large number of derivatives of the penicillin (e.g., **449**)²⁹⁸ and cephalosporin (e.g., **450**)³⁰⁰ types have been prepared with *N*-acyl residues containing meso-ionic heterocyclic groupings. Some have shown antistreptococcal and antistaphylococcal activities *in vivo*.

b. *1,2,3-Oxadiazol-5-imines* (*Sydnone Imines*) (2). A number of different biological activities have been claimed for sydnone imines (2), their corresponding cations (3), and their *N*-acyl derivatives (4). The activities that have been listed include analgesics,^{338,339} anti-

³³¹ E. Goeres and A. Faehndrich, *Acta Biol. Med. Ger.* **20**, 641 (1968) [*CA* **69**, 50740m (1968)].

³³² Y. Imashiro and K. Masuda (Takeda Chem. Ind. Ltd.), Japan. 69 32,411 [*CA* **72**, 111482q (1970)].

³³³ K. Masuda and Y. Imashiro (Takeda Chem. Ind. Ltd.), Japan. 70 06,016 [*CA* **72**, 132745t (1970)].

³³⁴ D. P. Cameron and E. H. Wiseman, *J. Med. Chem.* **11**, 820 (1968).

³³⁵ E. Ackermann, *Acta Biol. Med. Ger.* **17**, 498 (1966) [*CA* **66**, 17865w (1967)].

³³⁶ H. D. Faulhaber, H. Spinner, P. Oehme, and K. Schwarz, *Folia Haematol.* **83**, 267 (1965) [*CA* **67**, 1969t (1967)].

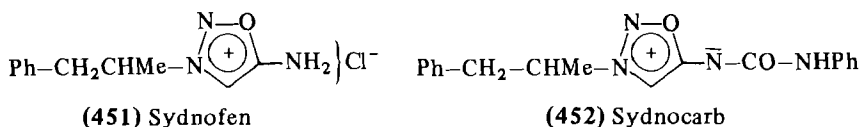
³³⁷ H. A. Wagner, (G. D. Searle and Co.), U.S. 3,524,859 [*CA* **73**, 131006m (1970)].

³³⁸ T. Kamitani and Y. Saito (Fujisawa Pharm. Co., Ltd.), Japan. 70 26,085 [*CA* **74**, 13165k (1971)]; T. Kamitani, Y. Saito, and T. Teraji (Fujisawa Pharm. Co., Ltd.), Japan. 70 26,086; 70 26,088; 70 26,089; 70 26,090 [*CA* **74**, 13164j; 13161f; 13166m; 13160e (1971)].

³³⁹ T. Kamitani, Y. Saito, and T. Terachi (Fujisawa Pharm. Co. Ltd.), Japan. 72 07,375 [*CA* **76**, 153751q (1972)].

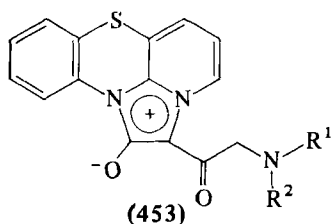
inflammatory agents,³³⁸⁻³⁴⁰ cardiovascular agents,³⁴¹⁻³⁵² central nervous system stimulants,^{340,353-362} and antidepressants.³⁶³

- ³⁴⁰ M. Ota (Takeda Chem. Ind. Ltd.), Japan. 70 06,015 [CA 73, 3918y (1970)].
- ³⁴¹ Y. Aramaki, M. Hirata, K. Masuda, and Y. Tanimoto (Takeda Chemical Industries, Ltd.), Japan. 6342 (1967) [CA 68, 29702v (1968)].
- ³⁴² K. Kikuchi, M. Hirata, A. Nagaoka, and Y. Aramaki, *Jap. J. Pharmacol.* 20, 23 (1970) [CA 73, 2425y (1970)].
- ³⁴³ M. Hirata and K. Kikuchi, *Jap. J. Pharmacol.* 20, 187 (1970) [CA 73, 64778z (1970)].
- ³⁴⁴ K. Masuda and Y. Imashiro (Takeda Chem. Ind., Ltd.), U.S. 3,312,690 [CA 67, 108662q (1967)].
- ³⁴⁵ K. Masuda, Y. Imashiro, and T. Kaneko, *Chem. Pharm. Bull.* 18, 128 (1970).
- ³⁴⁶ K. Kikuchi, M. Hirata, A. Nagaoka, and Y. Aramaki, *Jap. J. Pharmacol.* 20, 23 (1970) [CA 73, 2425y (1970)].
- ³⁴⁷ C. H. Boehringer, Sohn, Fr. Demande 2,004,770 [CA 72, 111479u (1970)].
- ³⁴⁸ M. Goetz, K. Freter, and K. Zeile (C. H. Boehringer, Sohn), Ger. Offen. 1,813,752 [CA 73, 66584g (1970)].
- ³⁴⁹ G. Wehlmann, K. Zeile, M. Goetz, and K. Freter, (C. H. Boehringer, Sohn), Ger. Offen. 1,942,854 [CA 73, 131005k (1970)].
- ³⁵⁰ K. Hashimoto, N. Taira, M. Hirata, and M. Kokubun, *Arzneim.-Forsch.* 21, 1329 (1971) [CA 76, 41952z (1972)].
- ³⁵¹ G. Regnier, R. Canevari, and M. Laubie (Science-Union et Cie.—Société Française de Recherche Médicale), Ger. Offen. 2,241,991 [CA 78, 159672c (1973)].
- ³⁵² M. Götz, K. Grozinger, and J. T. Oliver, *J. Med. Chem.* 16, 671 (1973).
- ³⁵³ L. E. Kholodov, I. F. Tishchenkova, R. A. Al'tshuler, V. G. Yashunskii, and M. D. Mashkovskii, *Khim.-Farm. Zh.* 2, 3 (1968) [CA 69, 96595w (1968)].
- ³⁵⁴ K. Masuda, Y. Imashiro, and T. Kamitani (Takeda Chem. Ind., Ltd.), Japan. 69 18,302 [CA 72, 3502n (1970)].
- ³⁵⁵ K. Masuda and Y. Imashiro (Takeda Chem. Ind., Ltd.), Japan. 70 06,265 [CA 73, 25485g (1970)].
- ³⁵⁶ V. G. Yashunskii, M. D. Mashkovskii, V. Z. Gorkin, L. E. Kolodov, R. A. Al'tshuler, A. I. Polezhaeva, and I. V. Verevkin, *Farmakol. Toksikol. (Moscow)* 33, 297 (1970) [CA 73, 54388h (1970)].
- ³⁵⁷ V. Z. Gorkin, V. G. Yashunskii, M. D. Mashkovskii, R. A. Al'tshuler, I. V. Verevkin, and L. E. Kholodov, *J. Med. Chem.* 14, 1013 (1971).
- ³⁵⁸ M. D. Mashkovskii, V. G. Yashunskii, R. Al'tshuler, L. E. Kholodov, G. Y. Avrutskii, Y. A. Aleksandrovskii, and A. B. Shmulevich (Ordzhonikidze, S., All-Union Sci. Res. Chem.-Pharm. Inst.), Ger. Offen. 2,028,880 [CA 76, 72521n (1972)].
- ³⁵⁹ M. D. Mashkovskii, R. A. Al'tshuler, G. Y. Avrutskii, Y. A. Aleksandrovskii, and R. L. Smulevich, *Zh. Nevropatol. Psichiat. im. S.S. Korsakova* 71, 1704 (1971) [CA 76, 81319e (1972)].
- ³⁶⁰ S. Ordzhonikidze, All-Union Sci.-Res. Chem.-Pharm. Inst., Fr. M. 8171 [CA 78, 62182e (1973)].
- ³⁶¹ R. A. Al'tshuler, M. D. Mashkovskii, and L. F. Roshchina, *Farmakol. Toksikol. (Moscow)* 36, 18 (1973) [CA 78, 92685p (1973)].
- ³⁶² L. E. Kholodov, V. G. Yashunskii, R. A. Al'tshuler, M. D. Mashkovskii, L. F. Roshchina, S. I. Shershneva, F. Y. Leibel'man, O. N. Volzhina, L. S. Gorodetskii, and N. A. Petrova, *Khim.-Farm. Zh.* 7, 50 (1973) [CA 78, 119341n (1973)].
- ³⁶³ M. D. Mashkovskii, V. G. Yashunskii, R. A. Al'tshuler, L. E. Kholodov, G. Y. Avrutskii, Y. A. Aleksandrovskii, and A. B. Shmulevich (Ordzhonikidze, S., All-Union Sci.-Res. Chem. Pharm. Inst.), British Patent 1,262,830 [CA 76, 140836w (1972)].



Clinical trials have been carried out on sydnofen (451)³⁶⁰ and sydnocarb (452)³⁶³ as psychostimulants or antidepressants. These two potential pharmaceuticals are of Russian origin.

c. *1,3-Diazol-4-ones* (91). The chloroacetylation product of 1-azaphenothiazine has been condensed with various secondary amines giving basic polycyclic meso-ionic 1,3-diazol-4-one derivatives (453), some of which showed useful anthelmintic activity.³⁶⁴



d. *1,3-Thiazol-4-ones* (114). Derivatives of this group have been described as useful central nervous system stimulants and anti-inflammatory drugs.³⁶⁵

e. *1,3-Thiazol-4-imines* (124). Various salts (126) have been found to act as anti-inflammatory agents,³⁶⁶⁻³⁷¹ sedatives,^{366,367} and central nervous system stimulants.³⁶⁸⁻³⁷¹

f. *1,2,3-Triazol-4-ones* (176). The activity of these heterocycles as plant growth inhibitors has been described, and their use as pre- or post-emergence herbicides reported.³⁷²

g. *1,2,4-Triazol-3-ones* (200). The cycloaddition product (200, R¹ = R³ = Ph, R² = H) obtained from *N*-phenylsydnone and phenyl isocyanate has been reported as a psychostimulant and anti-inflammatory agent.¹³⁸ Bicyclic 1,2,4-triazolo-pyridines (209) and their

³⁶⁴ J. W. Steele, W. K. Anderson, and W. F. Trager, *Can. J. Pharm. Sci.* 7, 103 (1972); *Can. J. Chem.* 50, 1026 (1972).

³⁶⁵ M. Ota (Takeda Chem. Ind., Ltd.), Japan. 70 14,069 [CA 73, 77241u (1970)].

³⁶⁶ M. Ota (Takeda Chem. Ind., Ltd.), Japan. 15,581 (1966) [CA 66, 10948v (1967)].

³⁶⁷ M. Ota (Takeda Chem. Ind., Ltd.), Japan. 15,582 (1966) [CA 66, 10949y (1967)].

³⁶⁸ M. Ota (Takeda Chem. Ind., Ltd.), Japan. 70 06,014 [CA 73, 25444t (1970)].

³⁶⁹ M. Ota (Takeda Chem. Ind., Ltd.), Japan. 70 11,505 [CA 73, 45501n (1970)].

³⁷⁰ Takeda Chemical Industries Ltd., Japan. 73 11,711.

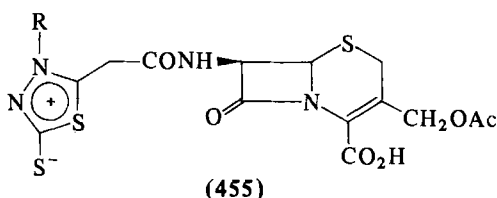
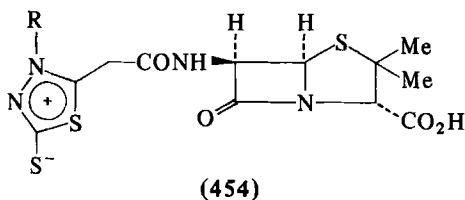
³⁷¹ Takeda Chemical Industries, Ltd., Japan. 73 11,712.

³⁷² W. Beil, H.-J. Wolff, A. Hoepfener, and H. C. Beil (Pfizer Inc.), DT 22239400.

tetrahydroderivatives have been claimed as analgesics and anti-inflammatory agents.³⁷³⁻³⁷⁷

h. *1,3,4-Thiadiazol-2-imines* (247). *N*-Acyl-thiadiazol-2-imines have been claimed as useful sedatives.³⁷⁸

i. *1,3,4-Thiadiazole-2-thiones* (251). The meso-ionic thiadiazoles^{4,158,159} show an interesting range of activities against gram-positive and gram-negative micro-organisms. Some derivatives also show cardiovascular effects.



Various derivatives of 6-aminopenicillanic acid (e.g., 454) and 7-aminocephalosporanic acid (e.g., 455) have been prepared and examined as possible antibacterials.³⁷⁹

j. *1,2,3-Thiadiazol-4-ones* (265). Recently the inhibition of monoamine oxidase by a series of meso-ionic 1,2,3-thiadiazol-4-ones (265) has been described.^{177,178} A model of enzyme-inhibitor interaction and an analysis of structural features controlling the mode of enzyme inhibition have been presented.¹⁷⁸

³⁷³ T. Kamitani and T. Teraike (Fujisawa Pharm. Co. Ltd.), Japan. 71 21,033 [CA 75, 118324k (1971)].

³⁷⁴ T. Kamitani and T. Teraike (Fujisawa Pharm. Co. Ltd.), Japan. 71 21,034 [CA 75, 129814w (1971)].

³⁷⁵ T. Teraji and T. Kamitani (Fujisawa Pharm. Co. Ltd.), Japan. 71 27,466 [CA 75, 151806s (1971)].

³⁷⁶ T. Teraji and T. Kamitani (Fujisawa Pharm. Co. Ltd.), Japan. 71 27,467 [CA 75, 118325m (1971)].

³⁷⁷ T. Teraji and T. Kamitani (Fujisawa Pharm. Co. Ltd.), Japan. 71 27,468 [CA 75, 151807t (1971)].

³⁷⁸ H. Koenig, P. Thieme, and A. Amann (Badische Anilin- und Soda-Fabrik A.-G.), Ger. Offen. 2,147,025 [CA 78, 159618q (1973)].

³⁷⁹ T. Takano and T. Kamitani (Fujisawa Pharm. Co. Ltd.), Japan. 71 25,747 [CA 76, 3876v (1972)].

k. *1,2,3,4-Oxatriazol-5-ones* (271). Their activity as hypotensive agents¹⁹² has been reviewed.⁴

l. *1,2,3,4-Oxatriazol-5-imines* (277). The *N*-acyl derivatives (277, $R^2 = Ac$)³⁸⁰ and the salts (285)³⁸¹ have been claimed as hypotensive agents.

XIII. Meso-ionic—Definition and Delineation

In the definition of the term meso-ionic as originally proposed by Baker and Ollis,² it was stated that "a compound may be appropriately called meso-ionic if it is a five- or possibly a six-membered heterocyclic compound which cannot be represented *satisfactorily* by any one covalent or polar structure and possesses a sextet of electrons in association with the atoms comprising the ring." This definition has formed the basis of this review, but we now propose a modification.

One hundred and forty-four meso-ionic heterocycles of type A (13, 19) and 84 meso-ionic heterocycles of type B (14, 20) are possible. The numbers of these two types which are now known (Table I: type A, 44 representatives) and (Table II: type B, 8 representatives) encourage us to put forward the proposal that the term meso-ionic should in future be restricted to five-membered heterocycles belonging to type A (13, 19) and type B (14, 20). This clear restriction upon the use of the term meso-ionic has obvious advantages. It still embraces 228 different classes of heterocycles with a common structural characteristic, and the many types of meso-ionic compounds included in the authoritative review by Ohta and Kato^{9b} are included. Needless to say, the restriction upon the definition of the term meso-ionic to five-membered heterocycles of type A and type B still includes, for example, benz derivatives such as the compounds 67, 71, 110, 123, 133, 151, 206, 209, 226, 255, and 258.

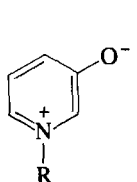
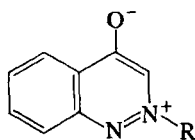
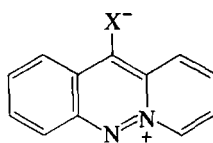
It is very important to emphasize that the terms meso-ionic compound and sydnone are not interchangeable. The term sydnone should be used only for the heterocyclic system (1). It just causes confusion if the word sydnone is used to describe other heterocyclic systems, although they are meso-ionic. The term sydnone should not be used to describe derivatives of 1,3,2-oxathiazol-5-one (169)¹¹⁷ and 1,2,3,4-tetrazole-5-thione (413).²⁴⁶

If heterocyclic chemists can be persuaded to restrict the use of the term "meso-ionic" only to five-membered heterocycles of type A and type B, then this will necessarily exclude some compounds that have

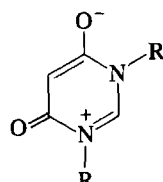
³⁸⁰ K. Masuda and T. Kamitani (Takeda Chem. Ind. Ltd.), Japan. 70 21,102 [CA 73, 87922f (1970)].

³⁸¹ K. Masuda and T. Kamitani (Takeda Chem. Ind. Ltd.), Japan. 70 20,904 [CA 73, 87930g (1970)].

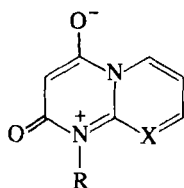
previously been described as meso-ionic. Acceptance of this suggestion would then mean that the term meso-ionic should no longer be used to

(456)³⁸²⁻³⁸⁵(457)³⁸⁶⁻³⁸⁸

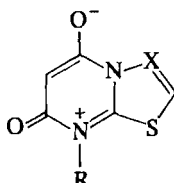
X = NR, O, S

(458)³⁸⁹(459)³⁹⁰⁻³⁹⁴

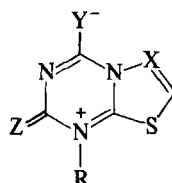
describe various six-membered heterocyclics (456-469)³⁸²⁻⁴¹¹ and a number of polyazapentalenes.⁴¹² These compounds (470-477)⁴¹³⁻⁴³² have been described as meso-ionic, but they are surely best regarded as mesomeric betaines and should be formulated and described as such.



X = CH, N

(460)^{395,396}

X = CH, N

(461)^{397,398}X = CH, N
Y, Z = O, S(462)³⁹⁹

³⁸² S. A. Harris, T. J. Webb, and K. Folkers, *J. Amer. Chem. Soc.* **62**, 3198 (1940).

³⁸³ A. R. Katritzky and Y. Takeuchi, *J. Amer. Chem. Soc.* **92**, 4134 (1970).

³⁸⁴ A. R. Katritzky and Y. Takeuchi, *J. Chem. Soc. C*, 874 (1971).

³⁸⁵ N. Dennis, A. R. Katritzky, T. Matsuo, S. K. Parton, and Y. Takeuchi, *J. Chem. Soc., Perkin Trans. I*, 746 (1974).

³⁸⁶ D. E. Ames and H. Z. Kucharska, *J. Chem. Soc.*, 4924 (1963).

³⁸⁷ E. Lunt and T. L. Threlfall, *Chem. Ind. (London)*, 1805 (1964).

³⁸⁸ D. E. Ames and B. Novitt, *J. Chem. Soc. C*, 2355 (1969).

³⁸⁹ R. Y. Ning, W. Y. Chen, and L. H. Sternbach, *J. Heterocycl. Chem.* **11**, 125 (1974).

³⁹⁰ M. Prystaš, *Collect. Czech. Chem. Commun.* **32**, 4241 (1967).

³⁹¹ T. Kappe and W. Lube, *Angew. Chem., Int. Ed. Engl.* **10**, 925 (1971).

³⁹² T. Kappe and W. Lube, *Monatsh. Chem.* **102**, 781 (1971).

³⁹³ Y. Maki, M. Sako, and M. Suzuki, *J. Chem. Soc., Chem. Commun.*, 999 (1972).

³⁹⁴ K. T. Potts and M. Šorm, *J. Org. Chem.* **37**, 1422 (1972).

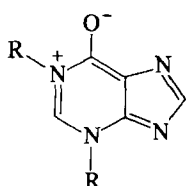
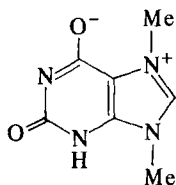
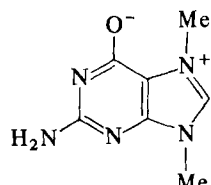
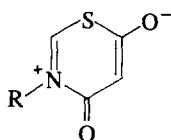
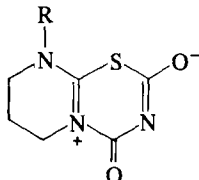
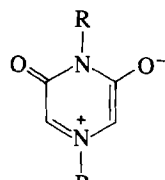
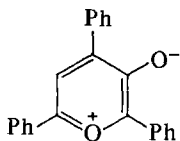
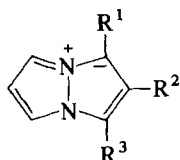
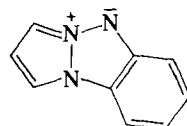
³⁹⁵ K. T. Potts and M. Šorm, *J. Org. Chem.* **36**, 8 (1971).

³⁹⁶ K. T. Potts and R. K. C. Hsia, *J. Org. Chem.* **38**, 3485 (1973).

³⁹⁷ R. A. Coburn and R. A. Glennon, *J. Heterocycl. Chem.* **10**, 487 (1973).

³⁹⁸ R. A. Coburn and R. A. Glennon, *J. Pharm. Sci.* **62**, 1785 (1973).

³⁹⁹ R. A. Coburn and B. Bhooshan, *J. Org. Chem.* **38**, 3868 (1973).

(463)⁴⁰⁰(464)⁴⁰¹(465)⁴⁰²(466)⁴⁰³(467)^{404,405}(468)⁴⁰⁶⁻⁴¹⁰(469)⁴¹¹(470)⁴¹³⁻⁴¹⁷(471)⁴¹⁵

4,8-Diazapentalenes

1,4,8-Triazapentalenes

⁴⁰⁰ R. A. Coburn and R. A. Carapellotti, *Tetrahedron Lett.*, 663 (1974).

⁴⁰¹ H. Brederick, G. Kupsch, and H. Wieland, *Chem. Ber.* **92**, 566 (1959).

⁴⁰² H. Brederick; O. Christmann, and W. Koser, *Chem. Ber.* **93**, 1206 (1960).

⁴⁰³ T. Kappe and W. Golser, *Synthesis*, 312 (1972).

⁴⁰⁴ H. Hagemann and K. Ley, *Angew. Chem., Int. Ed. Engl.* **11**, 1012 (1972).

⁴⁰⁵ H. Hagemann and K. Ley, *Angew. Chem.* **84**, 1063 (1972).

⁴⁰⁶ M. Ohta and H. Kato, *Nippon Kagaku Zasshi* **78**, 1400 (1957) [*CA* **54**, 511h (1960)].

⁴⁰⁷ R. Huisgen and H. Mäder, *Angew. Chem., Int. Ed. Engl.* **8**, 604 (1969).

⁴⁰⁸ J. Honzl and M. Šorm, *Tetrahedron Lett.*, 3339 (1969).

⁴⁰⁹ J. Honzl, M. Šorm, and V. Hanuš, *Tetrahedron* **26**, 2305 (1970).

⁴¹⁰ M. Šorm and J. Honzl, *Tetrahedron* **28**, 603 (1972).

⁴¹¹ K. T. Potts, A. J. Elliott, and M. Šorm, *J. Org. Chem.* **37**, 3838 (1972).

⁴¹² A. Matsumoto, J. H. Lee, and M. Yoshida, *Yuki Gosei Kagaku Kyokai Shi* **28**, 1097 (1970) [*CA* **74**, 87705h (1971)].

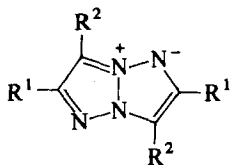
⁴¹³ T. W. G. Solomons and F. W. Fowler, *Chem. Ind. (London)*, 1462 (1963).

⁴¹⁴ T. W. G. Solomons, F. W. Fowler, and J. Calderazzo, *J. Amer. Chem. Soc.* **87**, 528 (1965).

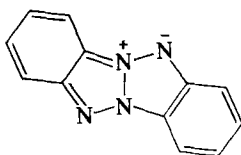
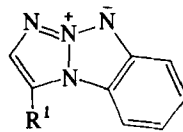
⁴¹⁵ S. Trofimenko, *J. Amer. Chem. Soc.* **87**, 4393 (1965); **88**, 5588 (1966).

⁴¹⁶ T. W. G. Solomons and C. F. Voigt, *J. Amer. Chem. Soc.* **87**, 5256 (1965); **88**, 1992 (1966).

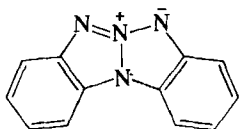
⁴¹⁷ V. Boekelheide and N. A. Fedoruk, *Proc. Nat. Acad. Sci. U.S.* **55**, 1385 (1966) [*CA* **65**, 13683d (1966)].

(472)⁴¹⁸⁻⁴²³

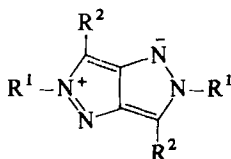
1,4,5,8-Tetrazapentalenes

(473)⁴²⁴⁻⁴²⁷(474)⁴²⁶⁻⁴²⁹

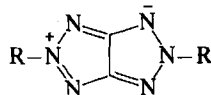
1,4,7,8-Tetrazapentalenes

(475)^{426,429}

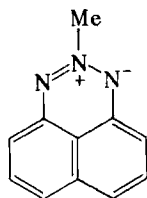
1,4,7,8-Tetrazapentalenes

(476)^{430,431}

1,2,5,6-Tetrazapentalenes

(477)⁴³²

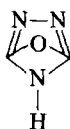
1,2,3,5,6,7-Hexazapentalenes

(478)⁴³³⁴¹⁸ R. Metze, *Angew. Chem.* **68**, 580 (1956).⁴¹⁹ R. Pflieger and H.-G. Hahn, *Chem. Ber.* **90**, 2411 (1957).⁴²⁰ R. Pflieger, E. Garthe, and K. Rauer, *Chem. Ber.* **96**, 1827 (1963).⁴²¹ R. Pflieger, E. Garthe, and K. Rauer, Ger. Offen. 1,620,103 [CA **75**, 49090s (1971)].⁴²² M. Brufani, W. Fedeli, G. Giacomello, and A. Vaciago, *Chem. Ber.* **96**, 1840 (1963).⁴²³ R. A. Carboni, J. C. Kauer, W. R. Hatchard, and R. J. Harder, *J. Amer. Chem. Soc.* **89**, 2626 (1967).⁴²⁴ R. A. Carboni and J. E. Castle, *J. Amer. Chem. Soc.* **84**, 2453 (1962).⁴²⁵ M. E. Burke, R. A. Sparks, and K. N. Trueblood, *Acta Crystallogr.*, **16**, A64 (1963).⁴²⁶ R. A. Carboni, J. C. Kauer, J. E. Castle, and H. E. Simmons, *J. Amer. Chem. Soc.* **89**, 2618 (1967).⁴²⁷ R. J. Harder, R. A. Carboni, and J. E. Castle, *J. Amer. Chem. Soc.* **89**, 2643 (1967).⁴²⁸ J. C. Kauer and R. A. Carboni, *J. Amer. Chem. Soc.* **89**, 2633 (1967).⁴²⁹ Y. T. Chia and H. E. Simmons, *J. Amer. Chem. Soc.* **89**, 2638 (1967).⁴³⁰ J. H. Lee, A. Matsumoto, O. Simamura, and M. Yoshida, *Chem. Commun.*, 1393 (1969).⁴³¹ A. Matsumoto, J. H. Lee, M. Yoshida, and O. Simamura, *Bull. Chem. Soc. Jap.* **47**, 946 (1974).⁴³² M. Yoshida, A. Matsumoto, and O. Simamura, *Bull. Chem. Soc. Jap.* **43**, 3587 (1970).⁴³³ M. J. Perkins, *J. Chem. Soc.*, 3005 (1964).

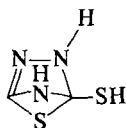
Other polyaza derivatives of aromatic systems, such as the blue triazaphthalene derivative (478),⁴³³ are also adequately described as meso-meric betaines or inner salts.

Ohta and Kato, in a section entitled "Bridged Heterocyclic Compounds" (ref. 9b, page 241), have referred to seven types of compounds and the stereochemically unacceptable structures (479–485) which had been allocated to them. The possibility was considered by Ohta and Kato that some of these structures might have to be replaced by their meso-ionic equivalents. However, we have now established⁴³⁴ that this is not the case, and the relation between the original structures (479–485) and the correct structures (486–492) is given in Fig. 10.

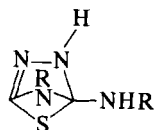
Original structural proposal^{9b}



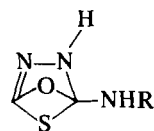
(479)



(480)

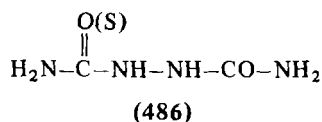


(481)

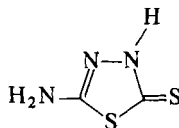


(482)

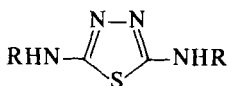
Correct structure⁴³⁴



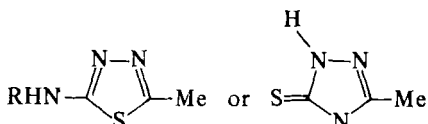
(486)



(487)



(488)



(489)

⁴³⁴ I. S. Smith, Ph.D. Thesis, University of Sheffield (1975).

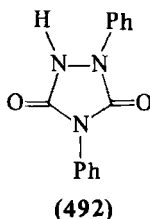
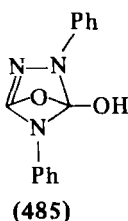
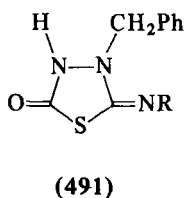
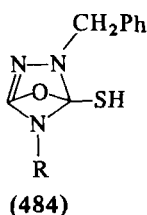
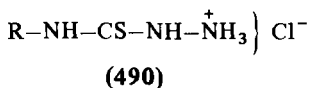
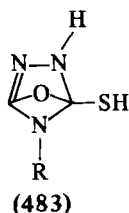
Original structural proposal^{9b}Correct structure^{43a}

FIG. 10. Correlation of original and correct structures of some "bridged heterocyclic compounds" reviewed by Ohta and Kato (Ref. 9b, page 241).

If our proposal for the restriction of the term "meso-ionic" finds general support and it is agreed that compounds exemplified by the structures (456–478) should not be called meso-ionic, then the definition we would wish to propose is as follows:

A compound may be appropriately called meso-ionic if it is a five-membered heterocycle which cannot be represented satisfactorily by any one covalent or polar structure and possesses a sextet of electrons in association with the five atoms comprising the ring.

Ohta and Kato, in 1969, in their useful and comprehensive review^{9b} on sydnone and other meso-ionic compounds, expressed their "strong desire to see the unfortunately chaotic present state of meso-ionic chemistry promptly rectified." We hope that this review covering the literature available to us up to September 1974 goes some way toward meeting their desire.

Appendix Added in Proof

The extent of current interest in meso-ionic chemistry is illustrated by the fact that since the completion of the manuscript of this review a number of significant papers have been published. These include descriptions of four new representatives of the type A meso-ionic heterocycles. Three of these systems belong to the 144 structural possibilities described in Section IV. This brings the number of known type A meso-ionic systems up to forty-seven. The fourth new system is the first example of a type A meso-ionic heterocycle having a selenium atom in the meso-ionic ring. The extension of the general formula **19** to include selenium provides the possibility of a further 176 type A meso-ionic systems of which one is now known. The structures of these four new meso-ionic systems are given in Table A-I (appendix to Table I).

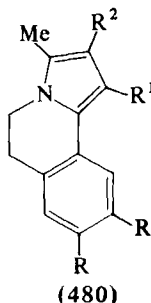
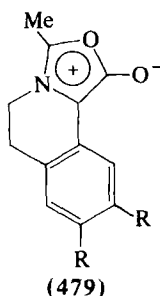
TABLE A-I

Parent System	Hetero- cycle	Atom or group					
		a	b	c	d	e	f
Oxazoles							
1,3-Oxazol-4-ones	481	NR	CR	O	CR	C	O
Oxathioles							
1,3-Oxathiol-4-ones	498	S	CR	O	CR	C	O
1,3-Oxathiol-5-ones	502	O	CR	S	CR	C	O
Selenazoles							
1,3-Selenazol-4-ones	505	NR	CR	Se	CR	C	O

This appendix covers the literature available to the reviewers up to September 1975. Section headings are used for easy reference to the main text. New headings are used for new classes of compounds.

SECTION VII, A

1. 1,3-Oxazol-5-ones (**66**) (page 16)

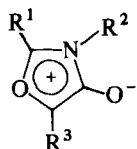


The ring fused pyrroles **480** have been prepared by *in situ* trapping of the meso-ionic 1,3-oxazol-5-ones (**479**) with alkynes. This 1,3-dipolar cycloaddition was found to be regiospecific when phenyl acetylene was used as 1,3-dipolarophile, the only products being **480**, $R^1 = \text{Ph}$, $R^2 = \text{H}$ or MeO , $R^1 = \text{Ph}$, $R^2 = \text{H}$.⁴³⁵

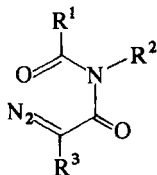
Polymers containing pyrrole units have been prepared by the *in situ* condensation of bis-1,3-oxazol-5-ones with diacetylenes.⁴³⁶

4. 1,3-Oxazol-4-ones (Anhydro-4-hydroxy-1,3-oxazolium Hydroxides) (**481**)

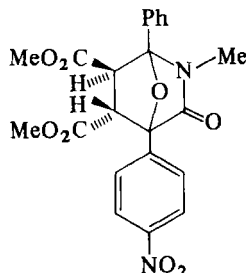
Representatives of this new class of meso-ionic heterocycles have been prepared by catalytic decomposition of the diazo compounds



(**481**) (See Table A-I)

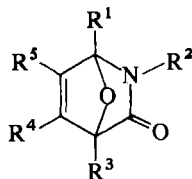


(**482**)



(**483**)

(**482**) using cupric acetylacetonate in hot benzene.^{437,438} For example, compound **481**, $R^1 = \text{Ph}$, $R^2 = \text{Me}$, $R^3 = \text{C}_6\text{H}_4\text{NO}_2$, m.p. $187^\circ\text{--}189^\circ$, was obtained as red crystals in 85% yield. These compounds readily participate in 1,3-dipolar cycloaddition reactions. The adduct **483** was formed in quantitative yield when compound **481**, $R^1 = \text{Ph}$, $R^2 = \text{Me}$, $R^3 = \text{C}_6\text{H}_4\text{NO}_2$, reacted with dimethyl fumarate in hot benzene. With acetylenic 1,3-dipolarophiles ($\text{R}^4\text{C}\equiv\text{CR}^5$), adducts of the general type **484** are readily formed together with furan derivatives, generated by loss of an isocyanate (R^2NCO) from the primary adduct **484**.^{437,438}



(**484**)

⁴³⁵ F. M. Hershenson, *J. Org. Chem.* **40**, 740 (1975).

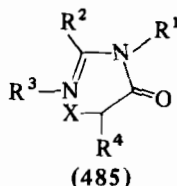
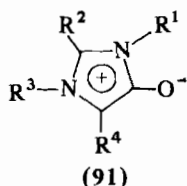
⁴³⁶ G. Manecke and J. Klawitter, *Makromol. Chem.* **175**, 3383 (1974).

⁴³⁷ M. Hamaguchi and T. Ibata, *Tetrahedron Lett.* 4475 (1974).

⁴³⁸ T. Ibata, M. Hamaguchi and H. Kiyohara, *Chem. Lett.* 21 (1975).

SECTION VII, B

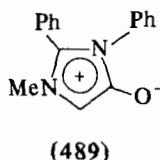
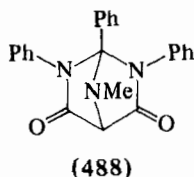
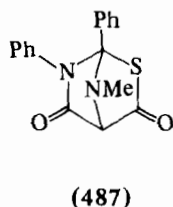
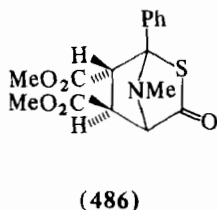
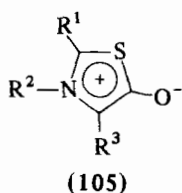
1. 1,3-Diazol-4-ones (91) (page 21)



A new method of preparing meso-ionic 1,3-diazol-4-ones (91) *in situ* has been described.⁴³⁹ Condensation of α -haloacyl chlorides ($R^4CHX.COCl$) with benzamidines ($R^2.C=NR^1.NHR^3$) in benzene solution gives α -haloacylamidines (485) which in the presence of triethylamine cyclize to the meso-ionic 1,3-diazol-4-ones (91). Using this procedure the 1,3-diazol-4-ones (91) were not isolated but evidence for their formation was provided by (i) the development of a yellow coloration and (ii) the formation of pyrroles in good yield by 1,3-dipolar cycloaddition of alkynes.⁴³⁹

SECTION VII, C

1. 1,3-Thiazol-5-ones (105) (page 24)



A full account of the preparation and 1,3-dipolar cycloaddition reactions of this class of meso-ionic heterocycle (105) has now been published.⁴⁴⁰ Using olefinic dipolarophiles or heterocumulenes, a number

⁴³⁹ M. Hamaguchi and T. Ibata, *Chem. Lett.* 169 (1975).

⁴⁴⁰ K. T. Potts, J. Baum, E. Houghton, D. N. Roy, and U. P. Singh, *J. Org. Chem.* **39**, 3619 (1974).

of structurally interesting 1 : 1 bicyclic adducts have been prepared. For example, with dimethyl fumarate in benzene compound **105**, $R^1 = \text{Ph}$, $R^2 = \text{Me}$, $R^3 = \text{H}$, gave the adduct **486**. The same derivative with phenyl isocyanate at 100° gave the primary adduct **487** (11%) and also the adduct **488** (48%). Compound **488** is formed by addition to the meso-ionic 1,3-diazol-4-one (**489**) (Section VII,B,1) which is almost certainly generated by loss of carbonyl sulfide from the adduct **487**.⁴⁴⁰

4. 1,3-Thiazol-4-ones (**114**) (page 26)

A full account of the preparation and 1,3-dipolar cycloadditions of the meso-ionic 1,3-thiazol-4-ones (**114**) has now been published.⁴⁴¹

A detailed chemical and spectroscopic study of the stereochemistry of the 1 : 1 adducts of the 1,3-thiazol-4-ones (**114**) with olefinic 1,3-dipolarophiles has been reported.⁴⁴²

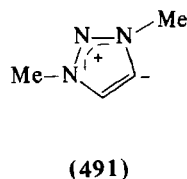
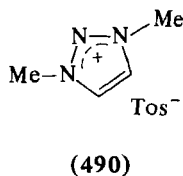
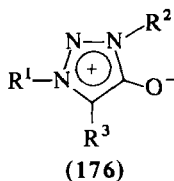
SECTION VII, E

1. 1,3,4-Oxadiazol-2-ones (**146**) (page 32)

The kinetics of the acid hydrolysis of isosydnone (**146**) to *N*-acylhydrazines (**147**, $X = \text{O}$) has been examined in detail and the mechanism has been discussed.^{443,444}

SECTION VII, G

1. 1,2,3-Triazol-4-ones (**176**) (page 38)



Treatment of 1,3-dimethyl-1,2,3-triazolium tosylate (**490**) with sodium hydride in dimethylformamide gives the ylide (**491**). Oxidation of this ylide (**491**) using oxygen and cupric chloride catalyst gave the meso-ionic 1,2,3-triazol-4-one **176**, $R^1 = R^2 = \text{Me}$, $R^3 = \text{H}$.⁴⁴⁵

⁴⁴¹ K. T. Potts, E. Houghton, and U. P. Singh, *J. Org. Chem.* **39**, 3627 (1974).

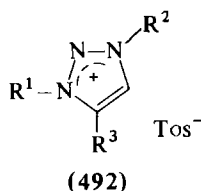
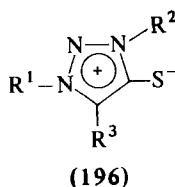
⁴⁴² K. T. Potts, J. Baum, and E. Houghton, *J. Org. Chem.* **39**, 3631 (1974).

⁴⁴³ A. J. Buglass and J. G. Tillett, *J. Chem. Soc., Perkin Trans. II*, 1687 (1973).

⁴⁴⁴ E. A. Isukul and J. G. Tillett, *J. Chem. Soc., Perkin Trans. II*, 230 (1975).

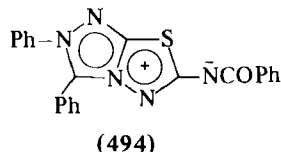
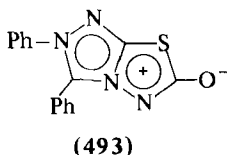
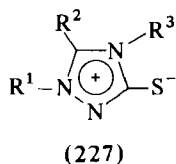
⁴⁴⁵ M. Begtrup, *J. Chem. Soc., Chem. Commun.* 334 (1975).

3. 1,2,3-Triazole-4-thiones (196) (page 42)



A new and convenient method of preparing the meso-ionic 1,2,3-triazole-4-thiones (196) has been reported. This involves the direct thiation of 1,3-disubstituted 1,2,3-triazolium tosylates (492) using sulfur and sodium hydride in dimethylformamide.⁴⁴⁶

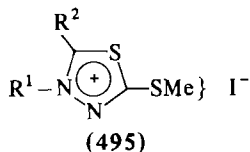
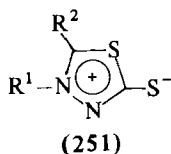
6. 1,2,4-Triazole-3-thiones (227) (page 47)



Treatment of the meso-ionic 1,2,4-triazole-3-thione, 227, $R^1 = R^2 = \text{Ph}$, $R^3 = \text{NH}_2$, with phosgene gives a novel bicyclic heterocyclic system which can be represented as a bicyclic meso-ionic 1,3,4-thiadiazol-2-one (493) (Section VII, H, 1). A similar reaction using *N*-benzoyl isocyanide dichloride ($\text{PhCO.N}=\text{CCl}_2$) gives the novel meso-ionic 1,3,4-thiadiazol-2-imine (494) (Section VII, H, 2).⁴⁴⁷

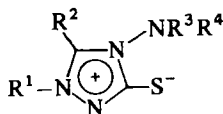
SECTION VII, H

3. 1,3,4-Thiadiazole-2-thiones (251) (page 52)

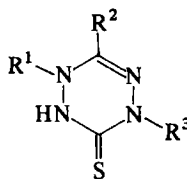


⁴⁴⁶ M. Begtrup, *Acta Chem. Scand.* **B29**, 141 (1975).

⁴⁴⁷ A. Ya. Lazaris, S. M. Shmulovich and A. N. Egorochkin, *Zh. Org. Khim.*, **10**, 2236 (1974) [*CA* **82**, 43270y (1975)].



(496)

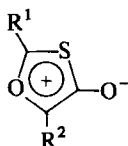


(497)

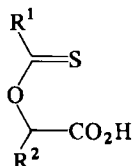
Predictably, treatment of the methiodides (**495**) with 1,1-disubstituted hydrazines ($R^3R^4N.NH_2$) gives the meso-ionic 1,2,4-triazole-3-thiones (**496**). An interesting variation is observed when the iodides (**495**) are treated with monosubstituted hydrazines ($R^3NH.NH_2$). In this case the product is a tetrazine (**497**).⁴⁴⁸

SECTION VII, L. OXATHIOLES

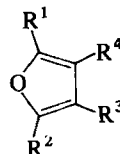
1. 1,3-Oxathiol-4-ones (Anhydro-4-hydroxy-1,3-oxathiolium Hydroxides) (**498**)



(498) (See Table A-1)

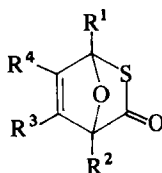


(499)



(500)

The meso-ionic 1,3-oxathiol-4-ones (**498**) are a new class of meso-ionic heterocycle which appear to be too unstable to be isolated at room temperature. They can be generated by cyclodehydration of the acids **499**, $R^1 = NR_2$, $R^2 = Ph$, using acetic anhydride, and trapped *in situ* by 1,3-dipolar cycloaddition with acetylenes; the product is a furan (**500**) formed via the bicyclic adduct (**501**).⁴⁴⁹

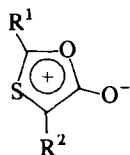


(501)

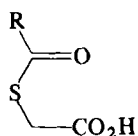
⁴⁴⁸ R. Grashey, C. Knorn, and M. Weidner, *Chem. Ztg., Chem. App.* **97**, 565 (1973) [*CA* **80**, 27223p (1974)].

⁴⁴⁹ H. Gotthardt, M. C. Weissshuhn, and K. Dörhöfer, *Angew. Chem. Int. Ed. Engl.* **14**, 422 (1975).

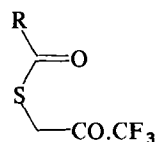
2. *1,3-Oxathiol-5-ones (Anhydro-5-hydroxy-1,3-oxathiolium Hydroxides) (502)*



(502) (See Table A-I)



(503)

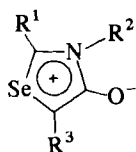


(504)

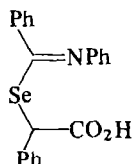
Representatives of this new type of meso-ionic system (502) have been prepared by cyclodehydration of the acid derivatives 503 using trifluoroacetic anhydride.⁴⁵⁰ For example, the acid 503, R = *p*.ClC₆H₄, gave the red crystalline meso-ionic 1,3-oxathiol-5-one (502, R¹ = *p*.Cl.C₆H₄, R² = CF₃.CO) which is readily hydrolysed to the ketone (504, R = *p*.Cl.C₆H₄). The trifluoroacetyl group in the 4-position appears to be essential for the stability of the meso-ionic system (502).

SECTION VII, M. SELENAZOLES

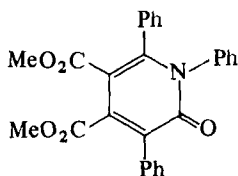
1. *1,3-Selenazol-4-ones (Anhydro-4-hydroxy-1,3-selenazolium Hydroxides) (505)*



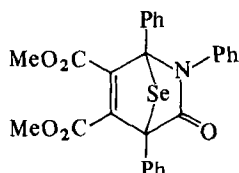
(505) (See Table A-I)



(506)



(507)



(508)

The α -selenoacid (506) with acetic anhydride-triethylamine at room temperature gave the meso-ionic 1,3-selenazol-4-one (505, R¹ = R² = R³ = Ph) as magenta needles in 80% yield.⁴⁵¹ This new meso-ionic

⁴⁵⁰ K. T. Potts, J. Kane, E. Carnahan, and U. P. Singh, *J. Chem. Soc., Chem. Commun.* 417 (1975).

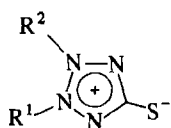
⁴⁵¹ M. P. Cava and L. E. Saris, *J. Chem. Soc., Chem. Commun.* 617 (1975).

system (**505**) appears to be only weakly reactive as a 1,3-dipole. When a benzene solution was heated under reflux with dimethyl acetylenedicarboxylate for one week, the pyridone diester (**507**) was formed. This product (**507**) is presumably formed by loss of selenium from the 1,3-dipolar cycloadduct (**508**).

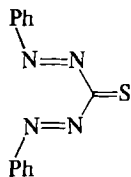
It is interesting to compare the mode of reaction of **505** with alkynes with that of the sulfur analog (**114**) whose mode of reaction depends upon the nature of the substituent in position 5 (see Section VII,C,4).

SECTION X, E

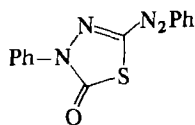
3. 1,2,3,4-Tetrazole-5-thiones (**413**) (page 84)



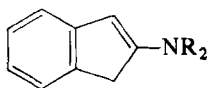
(413)



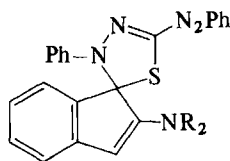
(415)



(509)



(510)



(511)

Two unusual transformations of dehydrodithizone (**413**, $R^1 = R^2 = \text{Ph}$) have been reported,^{452,453} and the structures of the products determined by X-ray crystallography. Both these reactions suggest that the dehydrodithizone (**413**, $R^1 = R^2 = \text{Ph}$) may well be reacting as its valence tautomer (**415**).

The first study⁴⁵² has shown that dehydrodithizone (**413**, $R^1 = R^2 = \text{Ph}$) reacts with pentacarbonyliron to give the 1,3,4-thiadiazol-2-one (**509**).

⁴⁵² P. N. Preston, N. J. Robinson, K. Turnbull, and T. J. King, *J. Chem. Soc., Chem. Commun.* 998 (1974).

⁴⁵³ G. V. Boyd, T. Norris, and P. F. Lindley, *J. Chem. Soc., Chem. Commun.* 100 (1975).

The second⁴⁵³ has shown that ynamines of the general type **510** ($\text{NR}_2 = \text{pyrrolidino, piperidino, morpholino}$) combine with dehydrodithizone (**413**, $\text{R}^1 = \text{R}^2 = \text{Ph}$) in chloroform at room temperature giving the red crystalline *spiro 1H-indene-1,2'-(3'H)-1,3,4-thiadiazoles* (**511**). The mode of formation of **511** is not clear but a reasonable mechanism would appear to require participation by the acyclic valence tautomer (**415**).

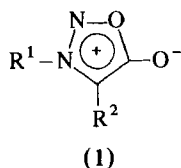
SECTION XI, A

The ionization potentials of four sydnones (**1**) have been compared with those of glycines and *N*-nitrosoglycines.⁴⁵⁴ The results suggest that in the gas phase the sydnones (**1**) exist as the nitrosoketen isomer (**47**).

SECTION XI, D

a. 1,2,3-Oxadiazol-5-ones (Sydnones) (**1**) (page 94)

A carbon-13 NMR study of four sydnones (**1**) has been reported.⁴⁵⁵ In 4-unsubstituted sydnones (**1**, $\text{R}^1 = \text{Me, Ph or PhCH}_2$, $\text{R}^2 = \text{H}$), the chemical shift of C-4 is substantially higher than has been measured for carbon in other unsubstituted heterocycles. This shielding of C-4 in the sydnone molecule is consistent with the results of *ab initio* and semi-empirical calculations which predict a high electron density at C-4.



A further CNDO study of 3-methylsydnone (**1**, $\text{R}^1 = \text{Me}$, $\text{R}^2 = \text{H}$) has been reported.⁴⁵⁶ The position of protonation and the mechanism of alkaline cleavage of 3-methylsydnone (**1**, $\text{R}^1 = \text{Me}$, $\text{R}^2 = \text{H}$) has been discussed in terms of CNDO/2 calculations.⁴⁵⁷

⁴⁵⁴ K. Undheim, M. A. F. El-Gendy, and T. Hurum, *Org. Mass. Spectrom.* **9**, 1242 (1974) [*CA* **83**, 27104n (1975)].

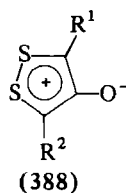
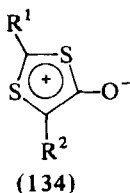
⁴⁵⁵ M. T. W. Hearn and K. T. Potts, *J. Chem. Soc., Perkin Trans. II*, 875 (1974).

⁴⁵⁶ J. Sauer and C. Jung, *Z. Phys. Chem. (Leipzig)*, **255**, 412 (1974).

⁴⁵⁷ E. V. Borisov, V. L. Lebedev and V. G. Yashunskii, *Zh. Fiz. Khim.*, **49**, 769 (1975) [*CA* **83**, 57860y (1975)].

b. *Other meso-ionic systems* (page 98)

PPP and CNDO/2 calculations have been reported for the 1,3-dithiol-4-ones (134) (Section VII,D,1) and the 1,2-dithiol-4-ones (338) (Section X,D,1).⁴⁵⁸



SECTION XII

a. *1,2,3-Oxadiazol-5-ones* (Sydnones) (1) (page 99)

New cephalosporin derivatives of the sydnones (1) have been prepared⁴⁵⁹ and some sydnones (1) useful as anti-inflammatory drugs have been described.^{460,461}

For a series of biologically active substituted 3-phenylsydnones, quantitative structure-activity relationships have been described.⁴⁶²

b. *1,2,3-Oxadiazol-5-imines* (Sydnone Imines) (2) (page 101)

Further studies on the preparation and activity of sydnofen (451)⁴⁶³ and sydnocarb (452)^{464,465} have been reported. A number of sydnone imine derivatives have also been described as useful hypotensive agents,⁴⁶⁶ vasodilators,⁴⁶⁶ muscle relaxants,⁴⁶⁶ and monoamine oxidase inhibitors.⁴⁶⁷

⁴⁵⁸ J. Fabian, *J. Prakt. Chem.*, **315**, 690 (1973).

⁴⁵⁹ M. Ochiai, O. Aki, A. Morimoto, and T. Okada (Takeda Chem. Ind., Ltd.), Ger. Offen. 2,429,135 [CA **82**, 156342s (1975)].

⁴⁶⁰ R. H. Wagner and J. B. Hill, *J. Med. Chem.*, **17**, 1337 (1974).

⁴⁶¹ J. B. Hill, R. E. Ray, R. H. Wagner, and R. L. Aspinall, *J. Med. Chem.*, **18**, 50 (1975).

⁴⁶² R. Franke, E. Gäbler, and P. Oehme, *Acta Biol. Med. Germ.*, **32**, 545 (1974).

⁴⁶³ Z. M. Bobritskaya, *Fiziol. Zh. (Kiev)*, **20**, 163 (1974) [CA **81**, 33442w (1974)].

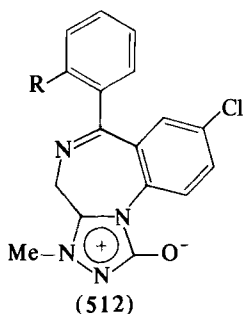
⁴⁶⁴ L. F. Roshchina, R. A. Al'tshuler, and M. D. Mashkovskii, *Farmakol. Toksikol. (Moscow)*, **38**, 263 (1975) [CA **83**, 71997e (1975)].

⁴⁶⁵ A. Y. Mekhedova and S. N. Luk'yanova, *Farmakol. Toksikol. (Moscow)*, **38**, 267 (1975) [CA **83**, 71998f (1975)].

⁴⁶⁶ K. Masuda and Y. Imashiro (Takeda Chem. Ind., Ltd.), U.S. 3,812,128 [CA **82**, 170958d (1975)].

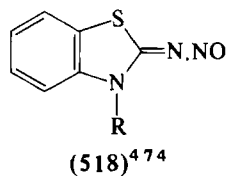
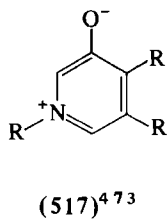
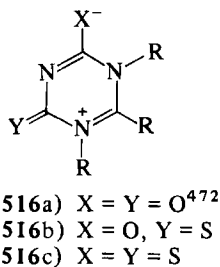
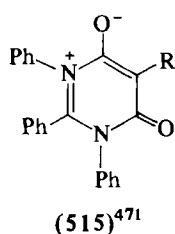
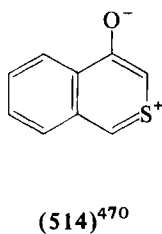
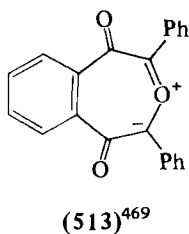
⁴⁶⁷ I. S. Slyusarenko, I. V. Verevkin, B. I. Bryantsev, V. Z. Gorkin, and V. G. Yashunskii, *Khim. Farm. Zh.*, **9**, 19 (1975) [CA **83**, 9926c (1975)].

g. 1,2,4-Triazol-3-ones (200) (page 103)



The derivatives 512 have been described as tranquilizers.⁴⁶⁸

SECTION XIII



⁴⁶⁸ J. B. Hester (Upjohn Co.) Ger. Offen. 2,441,436 [CA 83, 28296p (1975)].

⁴⁶⁹ H. Kato, K. Yamaguchi, and H. Tezuka, *Chem. Lett.*, 1089 (1974).

⁴⁷⁰ K. Undheim and S. Baklien, *J. Chem. Soc., Perkin Trans. I*, 1366 (1975).

⁴⁷¹ T. Kappe and R. K. Zadeh, *Synthesis*, 247 (1975).

⁴⁷² R. A. Coburn and B. Bhooshan, *J. Heterocyc. Chem.*, 12, 187 (1975).

⁴⁷³ Y. Maki, M. Suzuki, T. Furuta, T. Hiramitsu, and M. Kuzuya, *Tetrahedron Lett.*, 4107 (1974).

⁴⁷⁴ K. Akiba, M. Hisoaka, N. Inamoto, T. Ohta, and H. Kuroda, *Chem. Lett.*, 347 (1975).

The compounds **513–517** have recently been described as meso-ionic.^{469–473} According to our modified definition of the term “meso-ionic” (page 110) these interesting compounds (**513–517**) should now be described as mesomeric betaines.

The heterocyclic nitrosoimines (**518**) have been described as meso-ionic.⁴⁷⁴ These compounds (**518**) are represented *satisfactorily* by a covalent structure (**518**) and are *not* therefore meso-ionic.

References Added in Proof (January 1976)

The following references^{475–489} extend the literature coverage up to December 31, 1975. The preparation⁴⁷⁵ of derivatives of one previously unknown type A meso-ionic system has come to the attention of the authors since the completion of the Appendix. These new meso-ionic compounds⁴⁷⁵ are 1,2,3-thiadiazole-5-ones [Table A-I (page 111): a = S, b = N, c = NR, d = CR, e = C, f = O]. They are the first examples of sulfur analogs of the sydnones (1).

⁴⁷⁵ S. I. Burmistrov and V. A. Kozinskii, *Zh. Org. Khim.* **10**, 891 (1974) [CA **81**, 13444v (1974)].

⁴⁷⁶ Section VII,A,1. H. Matsukubo and H. Kato, *J. Chem. Soc., Chem. Commun.*, 840 (1975); R. Verbruggen and H. G. Viehe, *Chimia* **29**, 350 (1975).

⁴⁷⁷ Section VII,C,3. Y. Tominaga, Y. Matsuda, and G. Kobayashi, *J. Pharm. Soc. Jap.* **95**, 980 (1975); P. B. Talukdar and A. Chakraborty, *Indian J. Chem.* **13**, 661 (1975).

⁴⁷⁸ Section VII,C,4. M. Baudy and A. Robert, *J. Chem. Soc., Chem. Commun.*, 23 (1976).

⁴⁷⁹ Section VII,F,1. A. Alemagna and T. Bacchetti, *Chim. Ind.* **54**, 1105 (1972).

⁴⁸⁰ Section VII,H,2. M. Gannon, J. E. McCormick, and R. S. McElhinney, *Proc. Roy. Irish Acad. Sect. B* **74**, 331 (1974); R. Grashey and M. Weidner, *Chem.-Zt., Chem. App.* **97**, 623 (1973).

⁴⁸¹ Section VII,H,3. R. Grashey, C. Knorn, and M. Weidner, *Chem.-Zt., Chem. App.* **97**, 565 (1973); R. Grashey and C. Knorn, *ibid* **97**, 566 (1973).

⁴⁸² Section XI,B. G. V. Boyd, C. G. Davies, J. D. Donaldson, J. Silver, and P. H. Wright, *J. Chem. Soc. Perkin Trans. II*, 1280 (1975); Y. Tominaga, C. Tamura, S. Sato, T. Hata, R. Natsuki, Y. Matsuda, and G. Kobayashi, *Chem. Pharm. Bull.* **21**, 1651 (1973).

⁴⁸³ Section XI,B,c. G. M. J. Schmidt, *Bull. Res. Council. Isr.* **1**, 121 (1951) [CA **46**, 2871 (1952)].

⁴⁸⁴ Section XI,D,a. E. V. Borisov, N. V. Gorskaya, V. G. Yashunskii, and L. K. Vasyanina, *Khim. Geterotsikl. Soedin.*, 1049 (1975) [CA **83**, 205381k (1975)].

⁴⁸⁵ Section XI,D,b. M. J. S. Dewar and I. J. Turchi, *J. Chem. Soc. Perkin Trans. II*, in press.

⁴⁸⁶ Section XII,e. E. F. Litzinger (Allied Chem. Corp.), U.S. 3,617,248 [CA **76**, 25284c (1972)].

⁴⁸⁷ Section XII,i. A. Amann, H. Koenig, P. C. Thieme, H. Giertz, and R. Kretzschmar (BASF A.-G.), Ger. Offen. 2,408,288 [CA **83**, 193341g (1975)].

⁴⁸⁸ Section XIII. R. A. Coburn, R. A. Glennon, and Z. F. Chmielewicz, *J. Med. Chem.* **17**, 1025 (1974).

⁴⁸⁹ *Historical Note.* Much of the early work on meso-ionic compounds was pioneered by Max Busch. It seems appropriate that the final reference in this review should recognize this important contribution. Max Busch (1865–1941), *Ber.* **74**, (A)225 (1941); *Sitzungsber. Phys.-Med. Soz. Erlangen* **72**, xxxiii (1941) [CA **44**, 3314h (1950)].

The Chemistry of Thienothiophenes and Related Systems

V. P. LITVINOV AND YA. L. GOL'DFARB

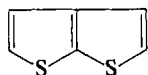
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Moscow, USSR*

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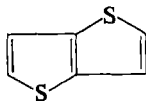
I. Introduction

The present review deals with condensed systems of heteroaromatic five-membered rings—thienothiophenes, dithienothiophenes, selenophenoselenophenes, and selenophenothiophenes. The number of publications devoted to such compounds has grown rapidly in recent years. This is indicative of the mounting interest in various aspects of this field of heterocyclic chemistry, which, however, has not been reviewed since the 1954 monograph of Hartough and Meisel.¹

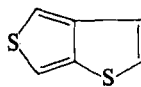
All isomeric thienothiophenes are now known: thieno[2,3-*b*]thiophene (1), thieno[3,2-*b*]thiophene (2), thieno[3,4-*b*]thiophene (3), and thieno[3,4-*c*]thiophene (4) (the last as a tetraphenyl-substituted derivative



(1)



(2)

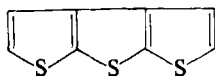


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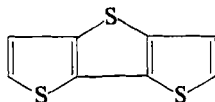


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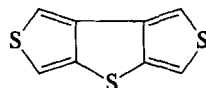
only); six isomeric dithienothiophenes—dithieno[2,3-*b*:3',2'-*d*]thiophene (5), dithieno[3,2-*b*:2',3'-*d*]thiophene (6), dithieno[3,4-*b*:3',4'-*d*]thiophene (7), dithieno[2,3-*b*:3',4'-*d*]thiophene (8), dithieno[3,2-*b*:3'4'-*d*]thiophene (9), and dithieno[2,3-*b*:2'3'-*d*]thiophene (10), three isomeric seleno-



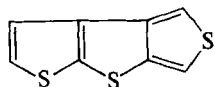
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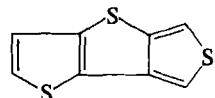
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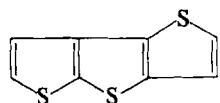
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(8)



(9)

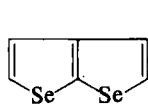


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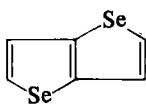
phenoselenophenes^{1a}—selenopheno[2,3-*b*]selenophene (11), selenopheno[3,2-*b*]selenophene (12), and selenopheno[3,4-*b*]selenophene

¹ H. D. Hartough and S. L. Meisel, "Compounds with Condensed Thiophene rings," pp. 10, 372, 458. Wiley (Interscience), New York, 1954.

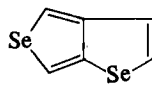
^{1a} The prefix "selenopheno" is used to denote selenophene fusion in this chapter, following the greater part of the literature in the field. *Chemical Abstracts* and the IUPAC Rules of Nomenclature prefer the (possibly confusing) form "selenolo." [Editors.]



(11)

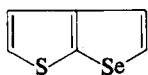


(12)

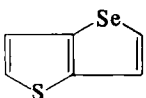


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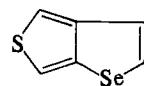
(13) and three isomeric selenophenothiophenes—selenopheno[2,3-*b*]-thiophene (14), selenopheno[3,2-*b*]thiophene (15), and selenopheno-



(14)



(15)



(16)

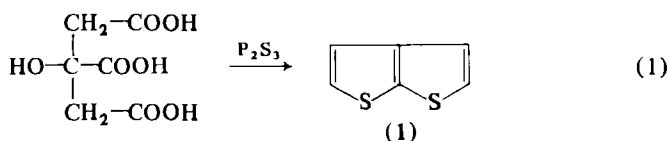
[2,3-*c*]thiophene (16)—have also been investigated, and are covered in this review, together with some related condensed systems. No reports have yet appeared on the fourth “classical” selenophenothiophene, the [3,4-*b*] isomer, or on any “nonclassical” [3,4-*c*]-fused selenophene.

II. Preparation of the Isomeric Thienothiophenes and Related Systems

According to the available literature, two main routes to the synthesis of isomeric thienothiophenes have been studied: cyclization of various aliphatic substances, and cyclization of derivatives of the thiophene series.

A. SYNTHESIS OF THIENOTHIOPHENES FROM ALIPHATIC COMPOUNDS

Soon after thiophene and its derivatives had been prepared by treating 1,4-dicarbonyl compounds with P_2S_3 , Biedermann and Jacobson² extended this procedure to citric and tricarballic acids. By heating a mixture of citric acid and P_2S_3 , they obtained a compound $C_6H_4S_2$, b.p. 224° – 226° , in about 1% yield. The structure 1 was ascribed to this compound, which was called thiophthene [Eq. (1)].



² A. Biedermann and P. Jacobson, *Ber.* **19**, 2444 (1886).

Similar results were obtained from the sodium salt of tricarballic acid with P_2S_3 .

In 1904 Oster³ obtained 1 in slightly higher yield by adding 10% of dry quartz sand to the mixture of citric acid and P_2S_3 . Hanna and Smith⁴ also prepared 1 by allowing P_2S_3 to react with sodium aconitate, but the yield remained very low.

A synthetic route developed by Capelle⁵ and deConinck⁶ in 1908 produced thienothiophene 1 in somewhat better yields. By passing acetylene through the vapors of boiling sulfur and then trapping the reaction products by carbon disulfide, they isolated, together with benzo[*b*]-thiophene, a compound, b.p. 225°, which formed a picrate similar to that obtained by Biedermann and Jacobson.²

Meyer *et al.*^{7,8} obtained in low yields thiophene, 2-methylthiophene, benzo[*b*]thiophene, traces of thienothiophene 1, and some other products on passing a mixture of acetylene, hydrogen (or methane), and hydrogen sulfide at 640°–670° through a tube filled with FeS_2 .

Later authors established the approximate composition of products formed in the reaction of acetylene with sulfur at different temperatures.^{9,10} At 325° the composition was found to be: CS_2 77%, thiophene 9%, thienothiophene 1 6%; at 500°, CS_2 77%, thiophene 12%, and thienothiophene 1 6%; at 650° CS_2 83%, thiophene 5%, and thienothiophene 1 3%, with sulfur conversion being 38%, 74%, and 77%, respectively. When studying this reaction at 290°–390°, Bhatt *et al.*¹¹ isolated thiophenol in addition to the above compounds but failed to increase the yield of thienothiophene 1.

The studies of Friedmann on the action of sulfur on octane¹² and octene¹³ under pressure are worth noting. Under such conditions about 2% of dimethylthienothiophene was formed together with thiophenes and other products. The author assumed the formation of the former to be due to octane isomerization. The product isolated was supposed to be 3,4-dimethylthieno[2,3-*b*]thiophene (17), which may result from the C_8 hydrocarbon rearrangement shown in Eq. (2).

³ H. Oster, *Ber.* 37, 3348 (1904).

⁴ D. C. Hanna and E. F. Smith, *J. Amer. Chem. Soc.* 21, 381 (1899).

⁵ G. Capelle, *Bull. Soc. Chim. Fr.* [4]3, 154 (1908).

⁶ W. O. deConinck, *Bull. Acad. Roy. Belg. Cl. Sci.*, 303 (1908) [*CA* 3, 643 (1909)].

⁷ R. Meyer and H. Wesche, *Ber.* 50, 422 (1917).

⁸ R. Meyer and W. Meyer, *Ber.* 51, 1571 (1918).

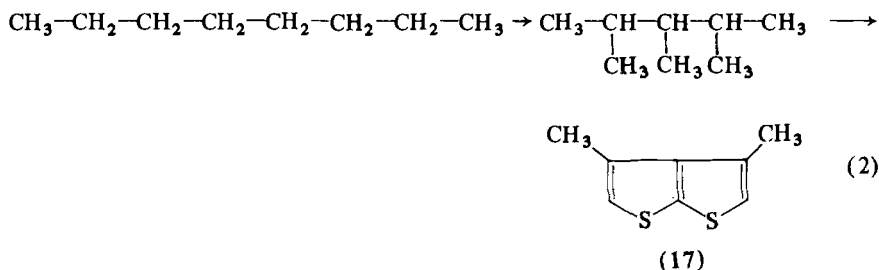
⁹ H. V. A. Briscoe and J. B. Pell, *J. Chem. Soc.*, 1741 (1928).

¹⁰ J. B. Pell and P. L. Robinson, *J. Chem. Soc.*, 2068 (1928).

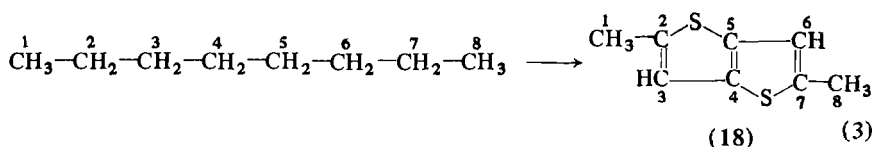
¹¹ C. T. Bhatt, K. S. Nargund, D. D. Kanga, and M. S. Shah, *J. Univ. Bombay* 3, 159 (1934) [*CA* 29, 4762 (1935)].

¹² W. Friedmann, *Ber.* 49, 1344 (1916).

¹³ W. Friedmann, *Ber.* 49, 1551 (1916).

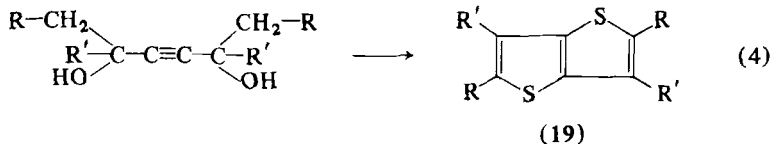


Horton,¹⁴ however, correctly observed that the product obtained by Friedmann could have the structure of thieno[3,2-*b*]thiophene (2) type rather than that of 1, since 2,5-dimethylthienol[3,2-*b*]thiophene (18) can be formed by ring closure through sulfur bridging without carbon chain isomerization [Eq. (3)].



For the reaction with *n*-heptane, Friedmann¹⁵ again postulated the hydrocarbon isomerization. He obtained two products, C₇H₁₀S (A) and C₇H₆S₂ (B). The structure of methylthieno[2,3-*b*]thiophene was ascribed to product B, though again there seems to be no reason to neglect the isomeric methylthieno[3,2-*b*]thiophene structure.

Studying the action of sulfur on hydrocarbons, Teste and Lozach^{16,17} showed that sulfur and P_2S_3 with 2,5-dimethyl-3-hexyne-2,5-diol resulted in the formation of 2,5-dimethylthienol[3,2-*b*]thiophene (19) ($R = Me$, $R' = H$) in very low yields, while with 3,6-dimethyl-oct-4-yne-3,6-diol they gave 2,3,5,6-tetramethylthienol[3,2-*b*]thiophene (19) ($R = R' = Me$) [Eq. (4)].



¹⁴ A. W. Horton, *J. Org. Chem.* **14**, 760 (1949).

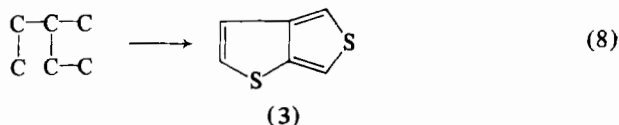
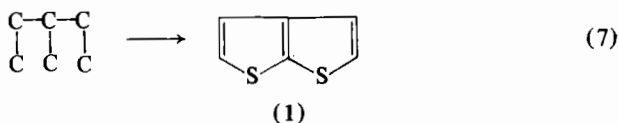
¹⁵ W. Friedmann, *Refiner Natural Gasoline Mfr.* 20, 395 (1941) [CA 36, 885 (1942)].

¹⁶ J. Teste and N. Lozac'h, *Bull. Soc. Chim. Fr.*, 422 (1955).

¹⁷ N. Lozac'h, *Sci. Ind. Chim. Belg.* **26**, 1137 (1961).

- ¹⁸ F. Challenger and J. B. Harrison, *J. Inst. Petrol. Technol.* **21**, 135 (1935).
- ¹⁹ F. Challenger, P. H. Clapham, and R. Emmot, *J. Inst. Petrol., London* **34**, 922 (1948).
- ²⁰ F. Challenger and R. Emmot, *J. Inst. Petrol., London* **37**, 396 (1951).
- ²¹ F. Challenger, *Sci. Progr.* **41**, 593 (1953).
- ²² J. Bruce, F. Challenger, H. B. Gibson, and W. E. Allenby, *J. Inst. Petrol., London* **34**, 226 (1948).
- ²³ D. J. Zwanenburg, H. de Haan, and H. Wynberg, *J. Org. Chem.* **31**, 3363 (1966).
- ²⁴ H. Wynberg and D. J. Zwanenburg, *Tetrahedron Lett.*, 761 (1967).
- ²⁵ F. Challenger, B. Fishwick, and J. L. Holmes, *Chem. Ind. (London)*, 519 (1952).
- ²⁶ F. Challenger and B. Fishwick, *J. Inst. Petrol., London* **39**, 220 (1953).

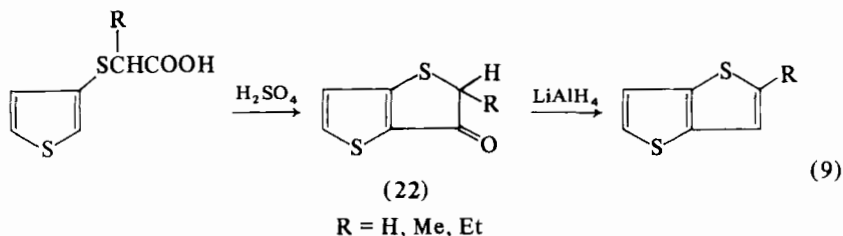
Challenger also assumed that both thienothiophenes 1 and 3 could be formed in the reaction of citric acid with P_2S_3 . This may be supported by the representations of the citric acid skeleton of Eqs. (7) and (8).



The formation of thieno[3,2-*b*]thiophene (2) together with thieno[2,3-*b*]thiophene (1) in reactions of citric acid with P_2S_3 or of acetylene with sulfur was first suggested by Anschütz and Rhodius.²⁷

B. SYNTHESIS OF THIENOTHIOPHENES FROM THIOPHENE DERIVATIVES

Challenger and Harrison¹⁸ found both thienothiophene 1 and its isomer 2 in the products of the reaction between acetylene and sulfur. To identify these compounds, Challenger *et al.*^{25,28} developed syntheses of unsubstituted and 2-alkyl-substituted thieno[3,2-*b*]thiophene (2) from thiophene derivatives. Cyclization of (3-thienylthio)acetic acid in the presence of sulfuric acid gave 2,3-dihydrothieno[3,2-*b*]thiophen-3-one (22) ($R = H$) in 14% yield; reducing the latter with lithium aluminum hydride resulted in thienothiophene (2) formation in 80% yield [Eq. (9)]. Similarly 2-methyl- and 2-ethyl-2,3-dihydrothieno[3,2-*b*]thiophen-3-one were obtained from α -(3-thienylthio)propionic and α -(3-thienylthio)butyric acids in 30% and 27% yields, respectively; their reduction yielded 2-methyl (32%) and 2-ethylthieno[3,2-*b*]thiophenes (52%). The parent acids were prepared from 3-mercaptothiophene.²⁹

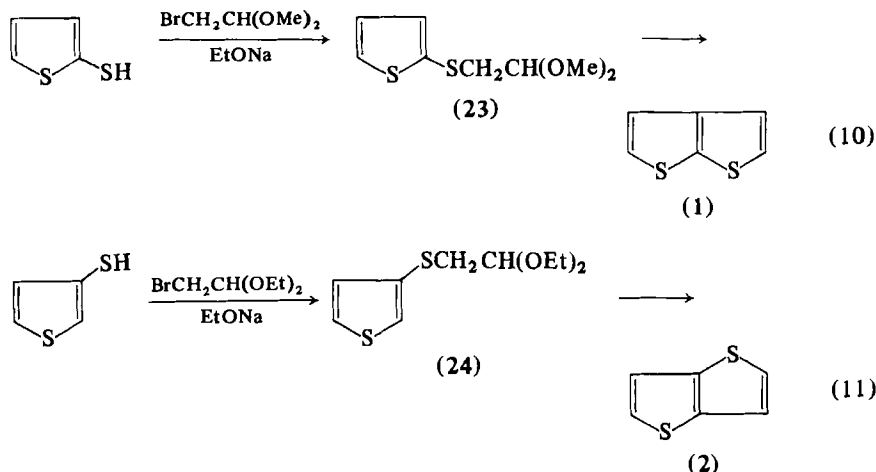


²⁷ R. Anschütz and E. Rhodius, *Ber.* 47, 2733 (1914).

²⁸ F. Challenger and J. L. Holmes, *J. Chem. Soc.*, 1837 (1953).

²⁹ F. Challenger, S. A. Miller, and G. M. Gibson, *J. Chem. Soc.*, 769 (1948).

When studying the carcinogenic activity of polycyclic hydrocarbons and their analogs containing thiophene rings (cf. Tilak³⁰), Tilak *et al.* synthesized both thienothiophene **1** and its isomer **2** in low yield from 2-thienyl dimethoxyethyl sulfide (**23**) and 3-thienyl diethoxyethyl sulfide (**24**), respectively, by the method developed for synthesis of thiophenes and thiopyrans^{31,32} [Eqs. (10) and (11)]. The compounds **23** and **24** were prepared from 2- and 3-mercaptothiophenes.^{30,33,34}



Another method for the preparation of aryl ω -dimethoxyethyl sulfides was described by Pandya and Tilak.^{30,35,36} The procedure consists in allowing aryl lithium derivatives to react with 2,2,2',2'-tetramethoxydiethyl disulfide. Subsequent cyclization of the sulfides by polyphosphoric acid yields 2–35% of condensed thiophenes and thiopyrans. By this method, thienothiophene **1** was prepared from 2-thienyllithium [Eq. (12)] and the previously unknown dithieno[2,3-*b*:3',2'-*d*]thiophene (**5**) was obtained from thienyl-2,5-dilithium. The possibility of synthesizing a heterocyclic analog (**25**) of pentacene from dithieno[2,3-*b*:3'2'-*d*]thiophene (**5**) [Eq. (13)] was suggested,³⁰ but seems not yet to have been realized.

³⁰ B. D. Tilak, *Tetrahedron* **9**, 76 (1960).

³¹ B. D. Tilak, *Proc. Indian Acad. Sci., Sect. A* **32**, 390 (1950).

³² K. Rabindran and B. D. Tilak, *Proc. Indian Acad. Sci., Sect. A* **36**, 411 (1952).

³³ V. V. Ghaisas and B. D. Tilak, *Current Sci* **22**, 184 (1953).

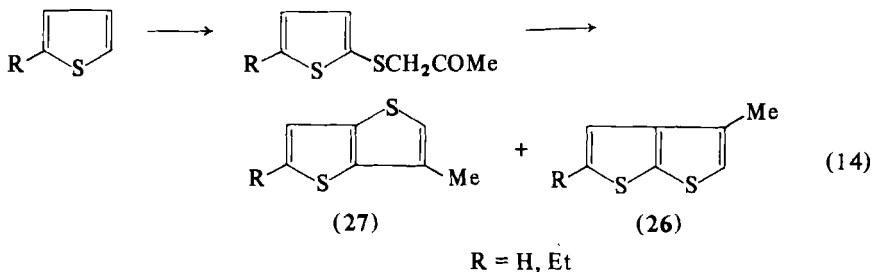
³⁴ V. V. Ghaisas and B. D. Tilak, *Proc. Indian Acad. Sci., Sect. A* **39**, 14 (1954).

³⁵ L. J. Pandya and B. D. Tilak, *Chem. Ind. (London)*, 981 (1958).

³⁶ L. J. Pandya and B. D. Tilak, *J. Sci. Ind. Res., Sect. B* **18**, 371 (1959).

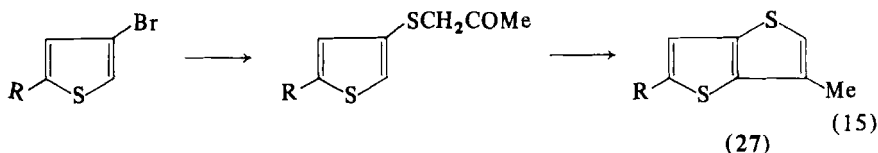
⁴² E. G. G. Werner, *Rec. Trav. Chim. Pays-Bas* **68**, 509 (1949).

however, that the cyclization product was a 60:40 mixture of 3-methyl-5-ethylthieno[2,3-*b*]thiophene (26) and 3-methyl-5-ethylthieno[3,2-*b*]thiophene (27) [Eq. (14)].



The mechanism of formation of two isomeric thienothiophenes by cyclization of 2-acetylthio-thiophenes in the presence of aluminum chloride may be as shown in Scheme 1.

Isomerization does not occur when the acetylthio group is in the thiophene β -position. Thus, 3-acetylthio-thiophene with aluminum chloride in benzene results only in alkyl-substituted thieno[3,2-*b*]thiophene (2) as shown by UV spectroscopy⁴³ and the identity of acetyl derivatives of the cyclization products with those of well established alkyl-substituted thienothiophene 2⁴⁴ [Eq. (15)].



Gronowitz *et al.*^{45,46} observed a similar isomerization of (2-pyrrolylthio)acetic acid to (3-pyrrolylthio)acetic acid by polyphosphoric acid followed by cyclization to 2,3-dihydrothieno[3,2-*b*]pyrrol-3-one.

Gronowitz and Moses⁴⁷ suggested that cyclization with simultaneous rearrangement may occur in compounds containing the thioglycolic acid

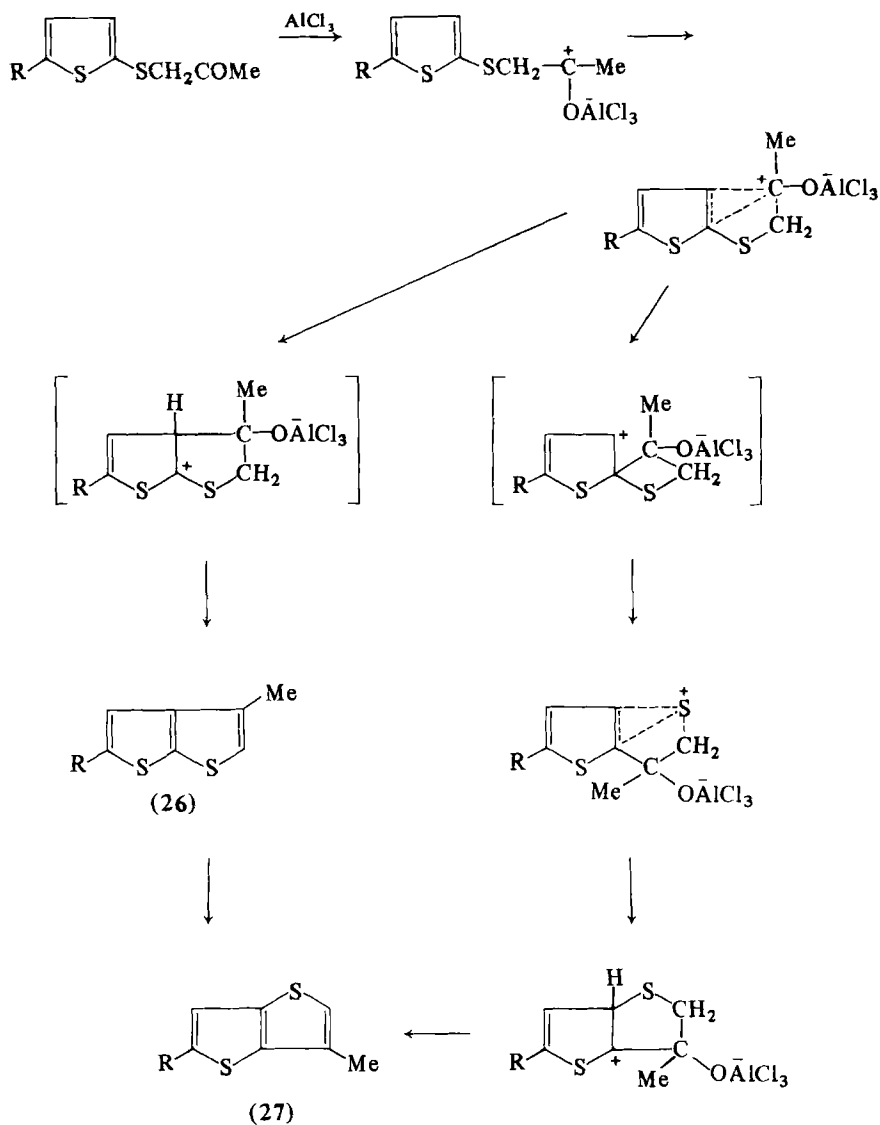
⁴³ Ya. L. Gol'dfarb, V. P. Litvinov, and S. A. Ozolin, *Izv. Akad. Nauk SSSR, Ser. Khim.* 510 (1965).

⁴⁴ Ya. L. Gol'dfarb and V. P. Litvinov, *Izv. Akad. Nauk SSSR, Otd. Khim. Nauk*, 352 (1963).

⁴⁵ S. Gronowitz, A.-B. Hörnfeldt, B. Gestblom, and R. A. Hoffman, *J. Org. Chem.* 26, 2615 (1961).

⁴⁶ S. Gronowitz, A.-B. Hörnfeldt, B. Gestblom, and R. A. Hoffman, *Ark. Kemi* 18, 151 (1961).

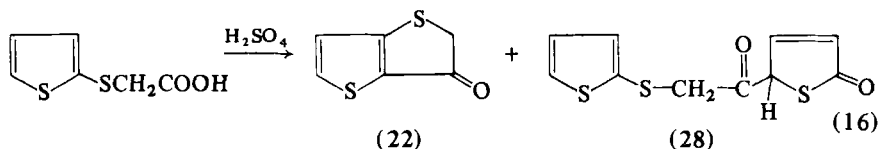
⁴⁷ S. Gronowitz and P. Moses, *Acta Chem. Scand.* 16, 155 (1962).



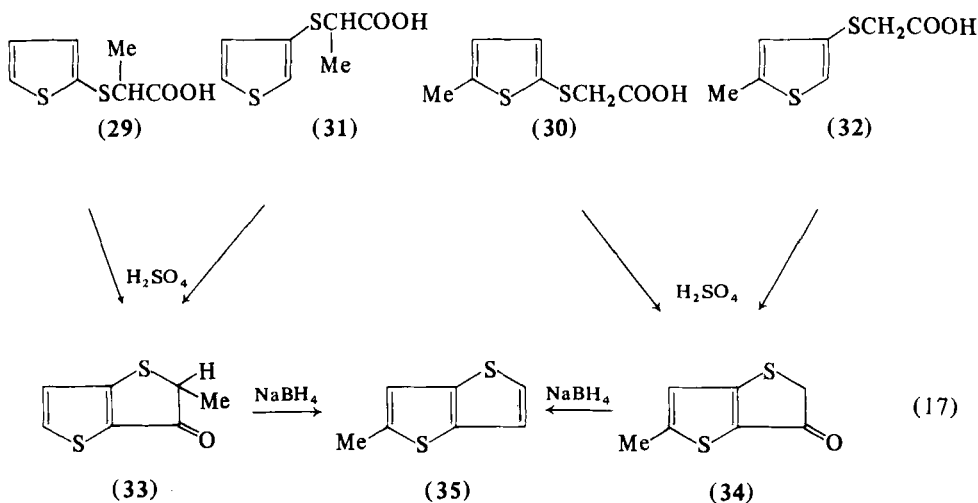
SCHEME 1

group in the position of the heteroaromatic ring most reactive to electrophilic substitution. They studied ring formation in the isomeric thienylthioacetic acids. Attempts to cyclize (2-thienylthio)acetic acid by polyphosphoric acid at 135° , by anhydrous HF at room temperature, or by the Friedel-Crafts method (acyl chloride in benzene in the presence

of stannic chloride) were unsuccessful. Only the Challenger method ^{25,28} (cyclization by concentrated sulfuric acid) [Eq. (16)] gave 9–11% of a mixture of 2,3-dihydrothieno[3,2-*b*]thiophen-3-one (22) and a ketone of supposed structure 28.



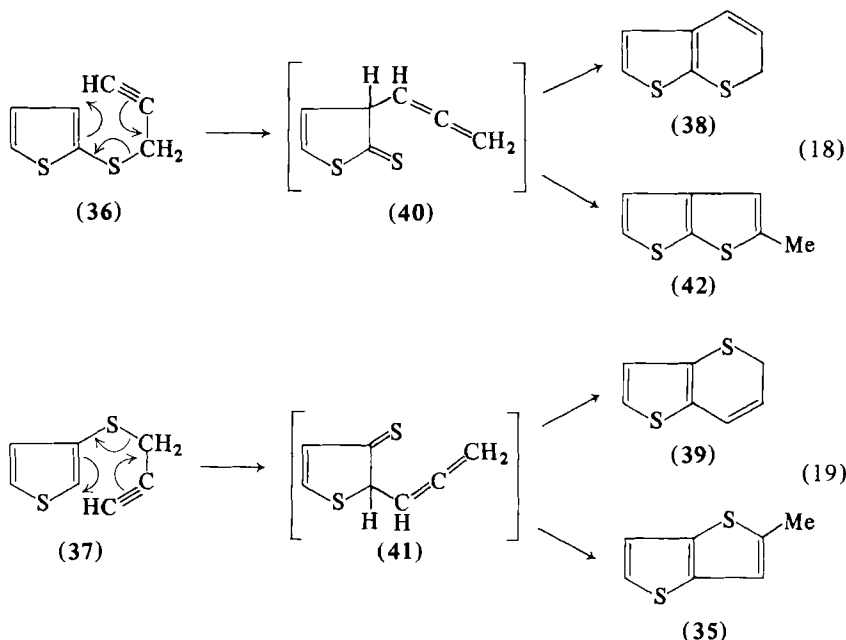
Gronowitz *et al.*,⁴⁸ studying the migration of a sulfide group catalyzed by concentrated sulfuric acid [Eq. (17)], found that cyclization of α -(2-thienylthio)propionic acid (29) or (5-methyl-2-thienylthio)acetic acid (30) by sulfuric acid also proceeds via isomerization to α -(3-thienylthio)propionic (31) or (5-methyl-3-thienylthio)acetic (32) acids, respectively. This is followed by the formation of 2-methyl-2,3-dihydrothieno[3,2-*b*]thiophen-3-one (33) or 5-methyl-2,3-dihydrothieno[3,2-*b*]thiophen-3-one (34). By reduction with sodium borohydride both compounds gave 2-methylthieno[3,2-*b*]thiophen (35). Cyclization of acids 31 and 32 under similar conditions was found to occur only to the 2-position of the thiophene ring, without rearrangement (cf. the data of other authors^{28,43}).



⁴⁸ S. Gronowitz, U. Ruden, and B. Gestblom, *Ark. Kemi* 20, 297 (1963).

It appears, therefore, that such a rearrangement may occur also during the polyphosphoric acid-catalyzed ring closure of 2-thienyl dimethoxyethyl sulfide (23). Thus, the method of Tilak *et al.*^{30,35,36} cannot be considered as an unambiguous route to a model thieno[2,3-*b*]-thiophene (1).

Another type of rearrangement of sulfides of the thiophene series was recently discovered by Brandsma *et al.*⁴⁹⁻⁵¹ and Lawesson *et al.*⁵² Good yields of thienothiopyran 38 and 39 were obtained by heating (2-propargylthio) (36) or (3-propargylthio) (37) thiophene, respectively, at 160°–170° in polar solvents [dimethyl sulfoxide (DMSO), dimethylformamide (DMF), quinoline, etc.]. A Claisen-type rearrangement was supposed⁴⁹ to be the first step of the cyclization, leading to the allene intermediates 40 and 41 shown in Eqs. (18) and (19). To obtain alkyl-substituted thienothiophenes, compounds 36 and 37 were treated with catalytic quantities of various secondary and tertiary amines in polar solvents. Besides thienothiopyrans 38 and 39, fair yields of 2-methylthieno[2,3-*b*]thiophene 42 and 2-methylthieno[3,2-*b*]thiophene (35), respectively, were obtained.⁵⁰



⁴⁹ L. Brandsma and H. J. T. Bos, *Rec. Trav. Chim. Pays-Bas* **88**, 732 (1969).

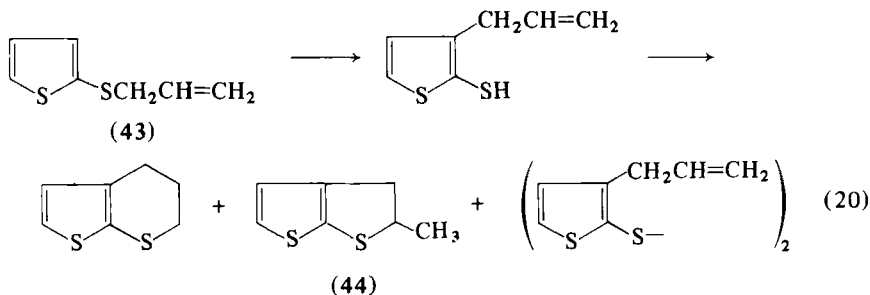
⁵⁰ L. Brandsma and D. Schuijl-Laros, *Rec. Trav. Chim. Pays-Bas* **89**, 110 (1970).

⁵¹ L. Brandsma, P. J. W. Schuijl, D. Schuijl-Laros, J. Meijer, and H. E. Wijers, *Int. J. Sulfur Chem., B* **6**, 85 (1971).

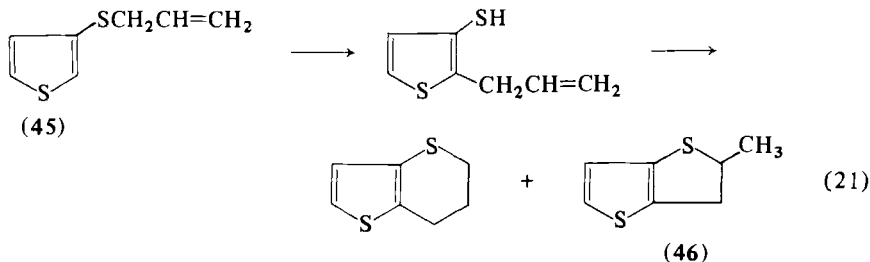
⁵² J. Z. Mortensen, B. Hedegaard, and S.-O. Lawesson, *Tetrahedron* **27**, 3831 (1971).

Secondary aliphatic amines were found to give higher yields of thienothiophenes than did tertiary amines, which are weaker bases. A maximum ratio of thienothiophenes to thienothiopyrans of about 4:1 was achieved at 145° with diisopropylamine as catalyst and DMSO as solvent. Only thienothiopyrans were formed in DMF in the presence of the same catalyst. The amines promote nucleophilic cyclization of Claisen rearrangement products into thienothiophenes. Since thienothiophenes are resistant to treatment with potassium *t*-butoxide in DMSO and thienothiopyrans form resinous products under these conditions, the method is a convenient route to pure thienothiophenes **35** and **42** in yields of up to 40%.⁵¹

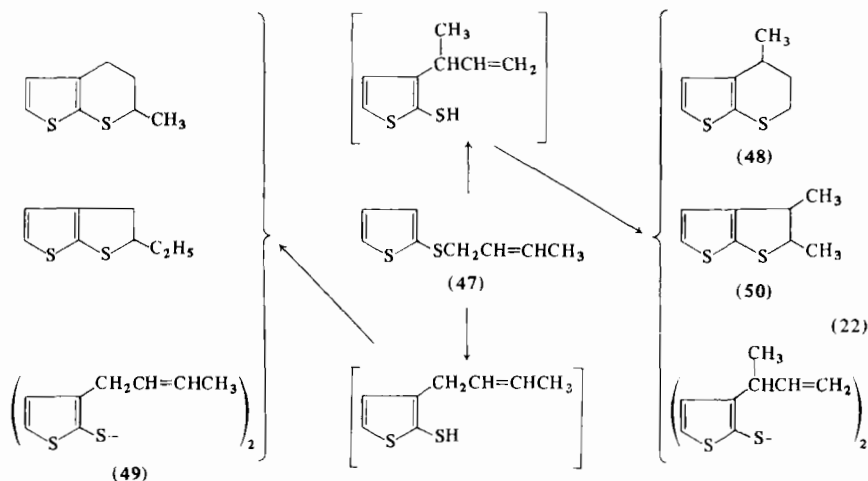
Lawesson *et al.*⁵² showed that allyl thienyl sulfides, when heated in quinoline, undergo a thio-Claisen-like rearrangement to give disulfides together with cyclization products both according and contrary to the Markovnikov rule. Thus, 2-methyl-2,3-dihydrothieno[2,3-*b*]thiophene (**44**) was obtained together with other products during allyl 2-thienyl sulfide (**43**) rearrangement [Eq. (20)].



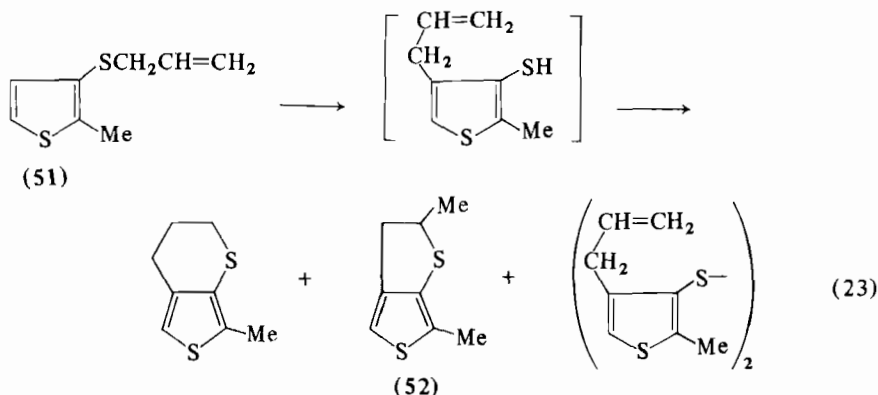
Rearrangement of allyl 3-thienyl sulfide (**45**) gives 2-methyl-2,3-dihydrothieno[3,2-*b*]thiophene (**46**) [Eq. (21)].



The rearrangement of crotyl 2-thienyl sulfide (**47**) at 200° gave only **48**, **49**, and 2,3-dimethyl-2,3-dihydrothieno[2,3-*b*]thiophene (**50**) out of numerous possibilities.

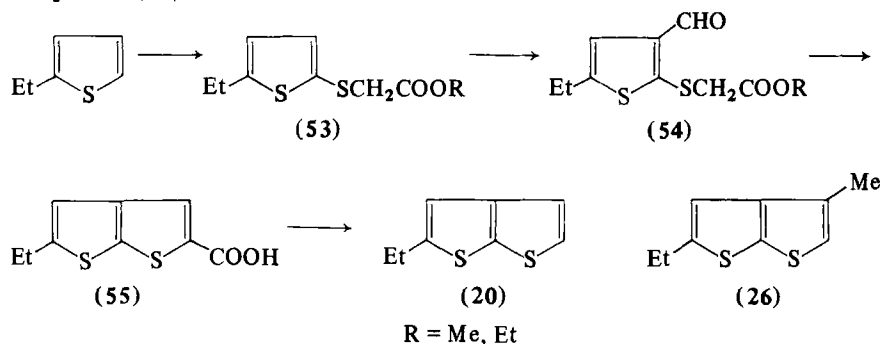


Thienyl sulfides with the 2-position of the thiophene ring blocked, e.g., allyl 2-methyl-3-thienyl sulfide (51), also undergo sigmatropic rearrangement when heated in quinoline [Eq. (23)]. 2,6-Dimethyl-2,3-dihydrothieno[3,4-*b*]thiophene (52) is formed, together with other products.



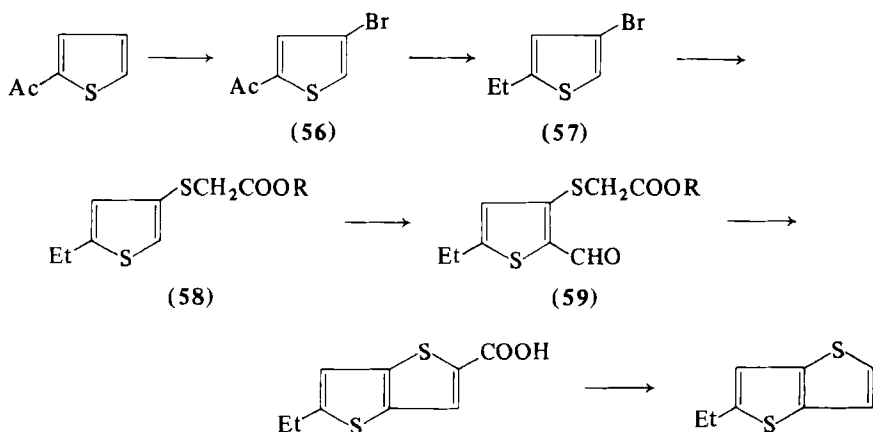
The authors of this review have developed a straightforward procedure for the synthesis of unsubstituted and alkyl-substituted thienothiophenes 1, 2, and 3; the method involves intramolecular condensation of ortho-bifunctional thiophene derivatives. Vilsmeier formylation of an alkyl (5-ethyl-2-thienylthio)acetate (53) furnishes the (5-ethyl-3-formyl-2-thienylthio)acetate (54) which when heated with alcoholic sodium

alkoxide gives 5-ethylthieno[2,3-*b*]thiophene-2-carboxylic acid (55) (>90% yield). On decarboxylation, acid 55 forms 2-ethylthieno[2,3-*b*]thiophene (20).^{41,53}



This method was useful for the synthesis of previously unknown α,β -dialkylthieno[2,3-*b*]thiophenes (26), by acetylating ($\text{AcCl}/\text{SnCl}_4$) rather than formylating.⁴⁴

The synthesis of alkylated thieno[3,2-*b*]thiophenes (2) via a similar procedure was also studied. As stated above, existing methods for the preparation of α -alkyl-substituted thienothiophene 2 derivatives and thienothiophene 2 itself are inefficient. The reduction of 4-bromo-2-acetothienone (56) (prepared by bromination of 2-acetothienone^{54,55})



SCHEME 2

⁵³ Ya. L. Gol'dfarb and V. P. Litvinov, *Izv. Akad. Nauk SSSR, Otd. Khim. Nauk*, 343 (1963).

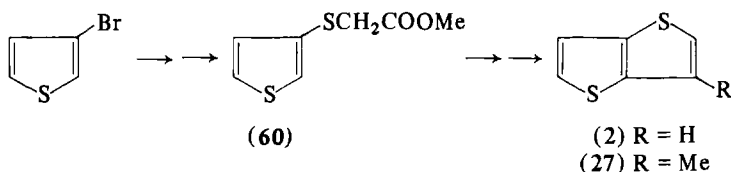
⁵⁴ Ya. L. Gol'dfarb, and Yu. B. Vol'kenstein, *Dokl. Akad. Nauk SSSR* 128, 536 (1959).

⁵⁵ Yu. B. Vol'kenstein, *Dissert.*, Moscow, 1962.

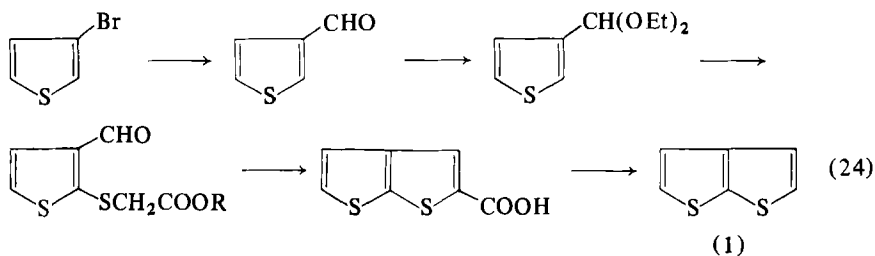
afforded 4-bromo-2-ethylthiophene (57), which was converted as described by Gronowitz⁵⁶ into (5-ethyl-3-thienylthio)acetate (58). The latter gave methyl (5-ethyl-2-formyl-3-thienylthio)acetate (59) on formylation; 59 was cyclized and decarboxylated⁵⁷ (Scheme 2).

Acetylation of ester (58) followed by treatment similar to that shown above resulted in 5-ethyl-3-methylthieno[3,2-*b*]thiophene (27).⁴⁴

Syntheses of unsubstituted thieno[3,2-*b*]thiophene (2) and 3-methylthieno[3,2-*b*]thiophene were carried out in a similar way;⁴³ metalation of 3-bromothiophene⁵⁸ with *n*-butyllithium at -70° and subsequent treatment with sulfur and methyl monochloroacetate gave methyl (3-thienylthio)acetate (60). Further reactions along the lines indicated above led to the thienothiophenes 2 and 27.



Ortho-bifunctional thiophenes provide the most convenient route to unsubstituted thieno[2,3-*b*]thiophene (1). 3-Bromothiophene yielded⁵⁹ 3-thiophenealdehyde. The corresponding diethyl acetal, using the procedure for thienothiophene 2, led to thieno[2,3-*b*]thiophene (1)^{60,61} in about 40% yield based on 3-bromothiophene [Eq. (24)]. This method was also used by Gronowitz and Persson⁶² for the synthesis of thienothiophene 1.



⁵⁶ S. Gronowitz, *Ark. Kemi* **13**, 269 (1958).

⁵⁷ V. P. Litvinov and Ya. L. Gol'dfarb, *Izv. Akad. Nauk SSSR, Ser. Khim.*, 2183 (1963).

⁵⁸ S. Gronowitz, *Acta Chem. Scand.* **13**, 1045 (1959).

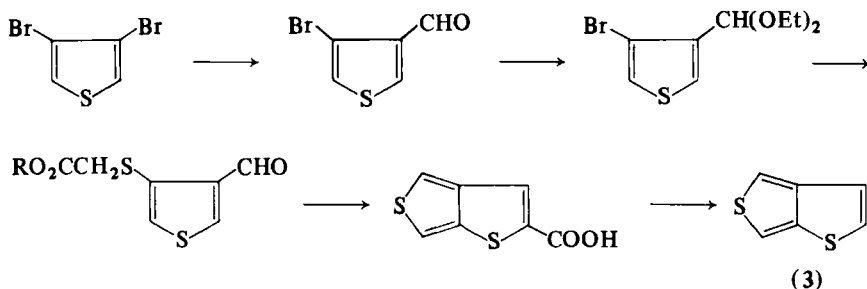
⁵⁹ S. Gronowitz, *Ark. Kemi* **8**, 441 (1956).

⁶⁰ Ya. L. Gol'dfarb, S. A. Ozolin, and V. P. Litvinov, *Khim. Geterotsikl. Soedin.*, 935 (1967).

⁶¹ Ya. L. Gol'dfarb, V. P. Litvinov, and S. A. Ozolin, in "Tezisy Dokladov XI Nauchn. Sessii po Khimii Seroorganich. Soyed. Neftei i Nefteproduktov," p. 30. Ufa, 1968.

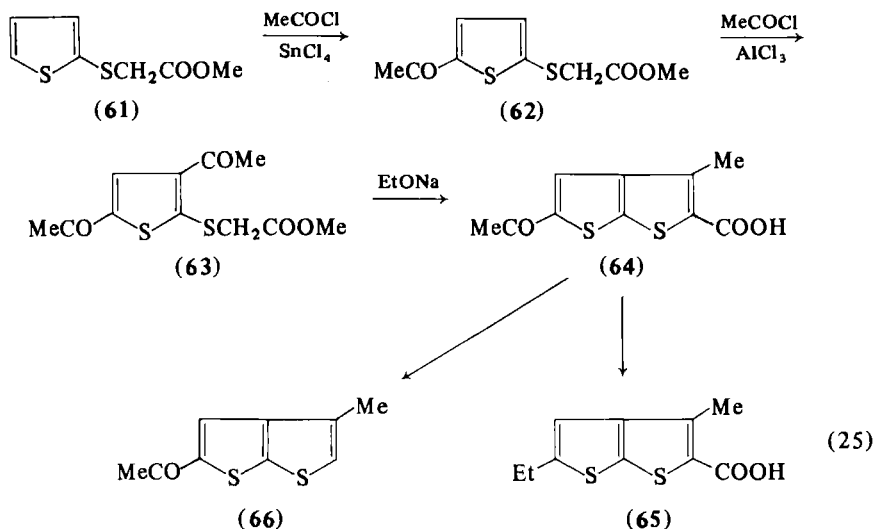
⁶² S. Gronowitz and B. Persson, *Acta Chem. Scand.* **21**, 812 (1967).

A similar method (Scheme 3) was used⁶³ for the third isomeric thienothiophene (3). 3,4-Dibromothiophene, obtained by debromination of 2,3,4,5-tetrabromothiophene,⁶⁴ was converted by the method of Gronowitz *et al.*⁶⁵ into 4-bromo-3-thiophenealdehyde and the corresponding acetal.



SCHEME 3

Introducing a second acyl group into monoacyl derivatives of the thiophene series by blocking the ketone group with excess aluminum chloride⁶⁶ opened another route to substituted thienothiophene 1.⁶⁷



⁶³ V. P. Litvinov and G. Fraenkel, *Izv. Akad. Nauk SSSR, Ser. Khim.*, 1828 (1968).

⁶⁴ S. Gronowitz, P. Moses, and R. Hakansson, *Ark. Kemi* 16, 267 (1960).

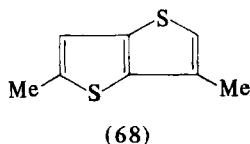
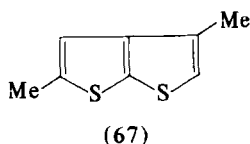
⁶⁵ S. Gronowitz, P. Moses, A.-B. Hörnfeldt, and R. Hakansson, *Ark. Kemi* 17, 165 (1961).

⁶⁶ Ya. L. Gol'dfarb and V. P. Litvinov, *Zh. Obshch. Khim.* 30, 2719 (1960).

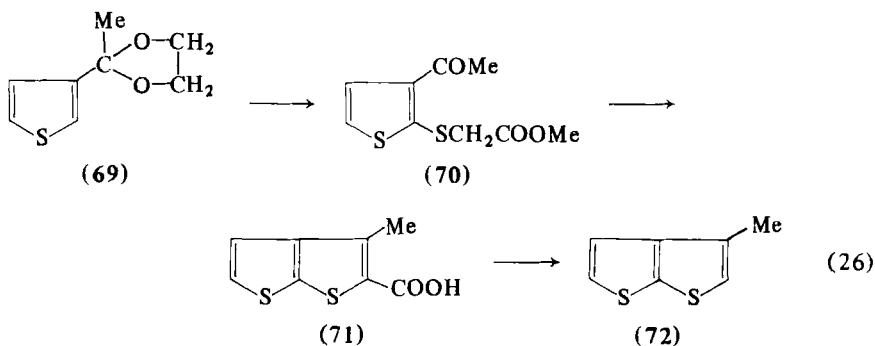
⁶⁷ Ya. L. Gol'dfarb, V. P. Litvinov, and S. A. Ozolin, *Izv. Akad. Nauk SSSR, Ser. Khim.*, 1432 (1966).

Thus, methyl (5-acetyl-2-thienylthio)acetate (**62**) was prepared by acetylation of **61**. Addition of a second acetyl group in the presence of excess AlCl_3 led to methyl (3,5-diacetyl-2-thienylthio)acetate (**63**), which, on heating in ethanolic sodium ethoxide yielded about 95% of 5-acetyl-3-methylthieno[2,3-*b*]thiophene-2-carboxylic acid (**64**); reduction of acid **64** resulted in 5-ethyl-3-methylthieno[2,3-*b*]thiophene-2-carboxylic acid (**65**), identical with the acid obtained by cyclization of methyl (3-acetyl-5-ethyl-2-thienylthio)acetate.⁴⁴ Decarboxylation of acid **64** gave 5-acetyl-3-methylthieno[2,3-*b*]thiophene (**66**) [Eq. (25)].

In this way Bugge⁶⁸ synthesized 2,4-dimethylthieno[2,3-*b*]thiophene (**67**) and 2,6-dimethylthieno[3,2-*b*]thiophene (**68**) from 2-methylthiophene and 4-bromo-2-methylthiophene.



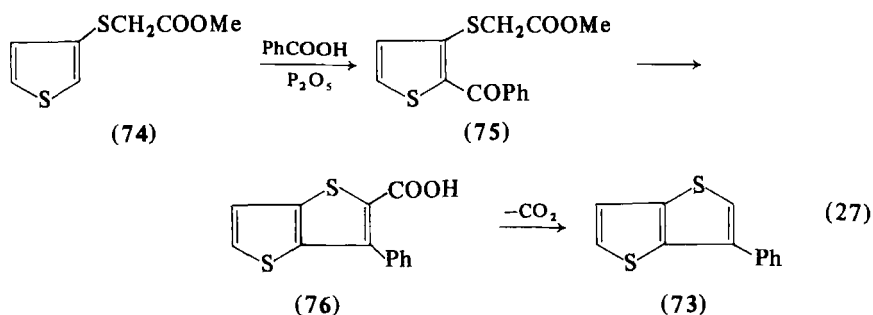
Bugge⁶⁸ also synthesized 3-methylthieno[2,3-*b*]thiophene (**72**) conveniently by metalation of 3-acetylthiophene ethylene ketal (**69**) followed by treatment with sulfur and methyl chloroacetate, cyclization of **70**, and decarboxylation of 3-methylthieno[2,3-*b*]thiophene-2-carboxylic acid (**71**) [Eq. (26)].



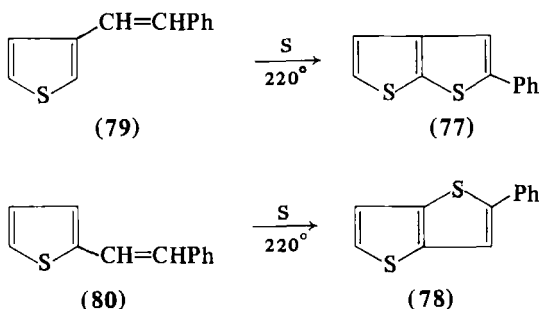
Italian authors⁶⁹ prepared 3-phenylthieno[3,2-*b*]thiophene (**73**) similarly. Methyl (2-benzoyl-3-thienylthio)acetate (**75**), obtained by benzoylating methyl (3-thienylthio)acetate (**74**), cyclized to 3-phenylthieno[3,2-*b*]thiophene-2-carboxylic acid (**76**) which was then decarboxylated [Eq. (27)].

⁶⁸ A. Bugge, *Acta Chem. Scand.* **25**, 27 (1971).

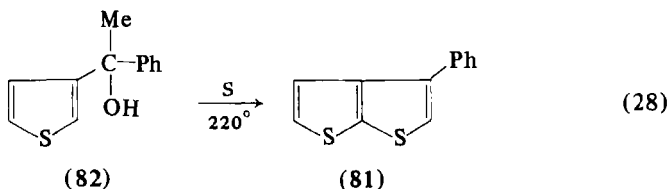
⁶⁹ P. Spagnolo, L. Testaferri, M. Tiecco, and G. Martelli, *J. Chem. Soc., Perkin Trans. I*, 93 (1972).



The reaction of 3-styrylthiophene (79) and 2-styrylthiophene (80) with sulfur at 220° led to 2-phenylthieno[2,3-*b*]thiophene (77) and 2-phenylthieno[3,2-*b*]thiophene (78).⁶⁹



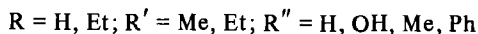
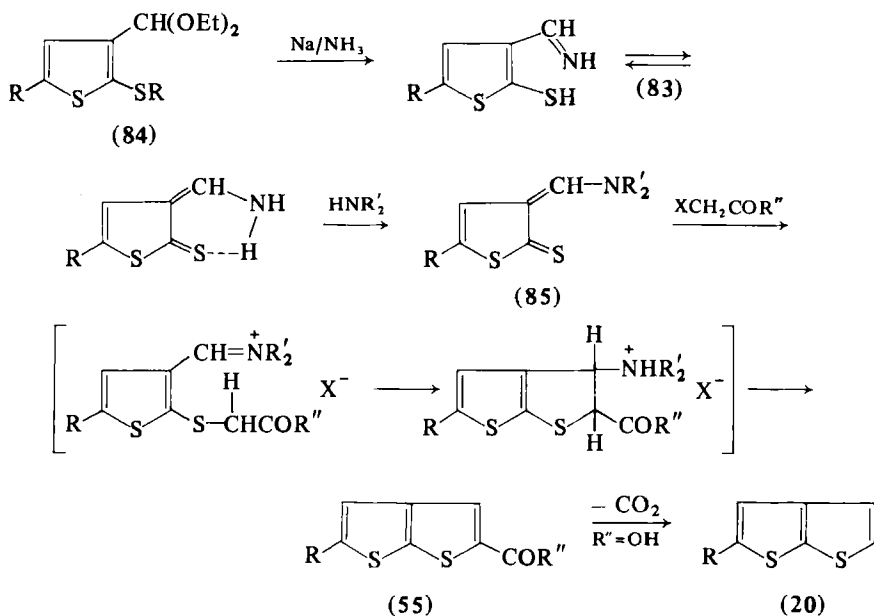
Similarly, 3-phenylthieno[2,3-*b*]thiophene (81) was produced from 1-phenyl-1-(3-thienyl)ethanol (82)⁶⁹ [Eq. (28)].



Gol'dfarb and Kalick⁷¹ showed that mercaptoaldimines (83) (cf. ref. 70), obtained from 5-alkyl-2-alkylmercapto-3-thiophenylaldehyde acetals (84) with sodium in liquid ammonia, gave *N,N*-dialkyl derivatives (85) in good yields with secondary aliphatic amines. The derivatives (85) with chloroacetic acid form 5-ethylthieno[2,3-*b*]thiophene-2-carboxylic acid (55), which readily decarboxylates to 2-ethylthieno[2,3-*b*]thiophene (20) (Scheme 4). Other α -halogen carbonyl compounds react with thione (85) ($R = Et$, $R' = Me$): with bromoacetone it gives 2-acetyl-5-ethylthieno[2,3-*b*]thiophene, with ω -bromoacetophenone, 2-benzoyl-5-ethylthieno-

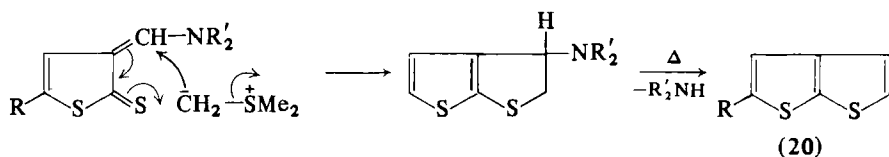
⁷⁰ Ya. L. Gol'dfarb and M. A. Kalick, *Usp. Khim.* 41, 679 (1972).

[2,3-*b*]thiophene, and with polymeric chloroacetaldehyde, it leads to 5-ethylthieno[2,3-*b*]thiophene-2-aldehyde, characterized as its 2,4-dinitrophenylhydrazone.



SCHEME 4

3-Dialkylamino-2,3-dihydrothieno[2,3-*b*]thiophenes are assumed intermediates as in Scheme 4. Such thiophenes are also formed in the reaction between thione (85) and dimethylsulfonium methylide (Scheme 5).⁷¹

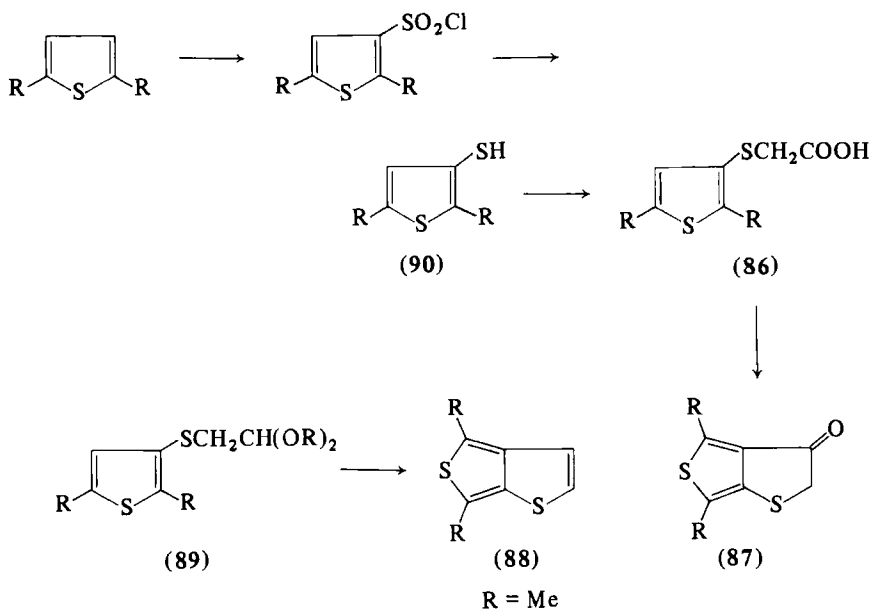


SCHEME 5

⁷¹ Ya. L. Gol'dfarb and M. A. Kalick, *Izv. Akad. Nauk SSSR, Ser. Khim.*, 2072 (1973).

As stated above, one of the routes to thienothiophene **2** is cyclization of (3-thienylthio)acetic acid in the presence of concentrated sulfuric acid followed by action of the 2,3-dihydrothieno[3,2-*b*]thiophen-3-one (**22**, R = H) formed with lithium aluminum hydride.^{26,28} Attempts by the present authors^{41,53} as well as those of Gronowitz and Moses⁴⁷ to obtain thienothiophene **1** by cyclizing (2-thienylthio)acetic acid or its chloride by various catalysts (stannic chloride, aluminum chloride or bromide, polyphosphoric acid or anhydrous HF) were unsuccessful. Synthesis of 2-ethyl-3-hydroxythieno[2,3-*b*]thiophene⁵³ by procedures commonly used for the preparation of 3-hydroxybenzo[*b*]thiophene⁷²⁻⁷⁴ also failed.

Dann and Dimmling showed⁷⁵ that (2,5-dimethyl-3-thienylthio)acetic acid (**86**) may be cyclized to 4,6-dimethyl-2,3-dihydrothieno[3,4-*b*]thiophen-3-one (**87**) by anhydrous hydrogen fluoride, and then reduced to 4,6-dimethylthieno[3,4-*b*]thiophene (**88**). The latter was obtained by cyclization of acetal (**89**) synthesized from 3-mercapto-2,5-dimethylthiophene (**90**) and bromoacetaldehyde dimethylacetal using hydrogen fluoride at 70°–80°. The synthetic route is illustrated by Scheme 6.



SCHEME 6

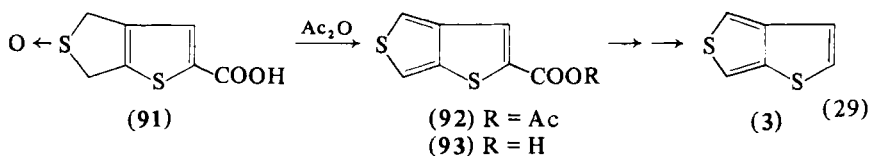
⁷² F. Krollpfeiffer and K. Scheider, *Ber.* **61**, 1284 (1928).

⁷³ German Patents 184,496, 200,200, 200,428; *Friedl.*, 555, 559, 560 (1911).

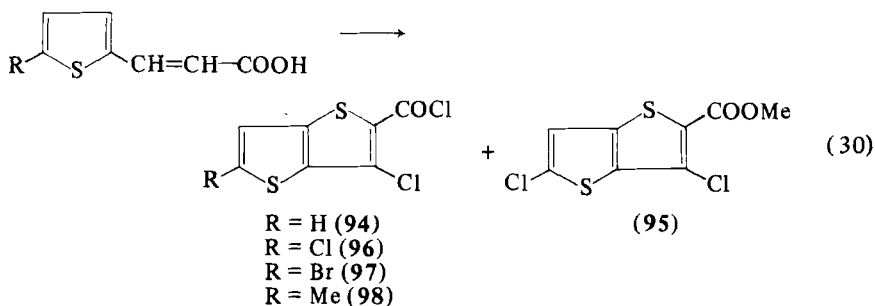
⁷⁴ K. Anwers and F. Arndt, *Ber.* **42**, 537 (1909).

⁷⁵ O. Dann and W. Dimmling, *Ber.* **87**, 373 (1954).

Unsubstituted thieno[3,4-*b*]thiophene (3) (see Litvinov and Fraenkel⁶³), was prepared by Cava and Pollack's⁷⁶ method for benzo[*c*]thiophene; i.e., thermal decomposition of 1*H*, 3*H*-benzo[*c*]thiophene sulfoxide. By refluxing 4*H*,6*H*-thieno[3,4-*b*]thiophene-2-carboxylic acid 5-oxide (91)²³ with acetic anhydride (the synthesis of dihydrothienothiophenes will be described below), Wynberg *et al.*^{24,77,78} obtained the mixed anhydride 92 in 95% yield. Hydrolysis gave thieno[3,4-*b*]thiophene-2-carboxylic acid (93) (88%). Decarboxylation of the acid (93) gave thienothiophene 3, unstable at room temperature [Eq. (29)].



In 1972 Wright⁷⁹ prepared 3-chlorothieno[3,2-*b*]thiophene-2-carbonyl chloride (94) in 11–13% yield by heating 3-(2-thienyl)acrylic acid, thionyl chloride, and pyridine, a method of synthesis of benzo[*b*]thiophene-2-carbonyl chloride derivatives.^{80–82} Methyl 3,5-dichlorothieno[3,2-*b*]thiophene-2-carboxylate (95) and methyl 2-chloro-3-(5-chloro-2-thienyl)acrylate were also isolated. When the reaction was carried out in refluxing toluene or chlorobenzene, the acid chloride (94)



⁷⁶ M. P. Cava and N. M. Pollack, *J. Amer. Chem. Soc.* **88**, 4112 (1966).

⁷⁷ H. Wynberg, J. Feijen, and D. J. Zwanenburg, *Rec. Trav. Chim. Pays-Bas* **87**, 1006 (1968).

⁷⁸ J. Feijen, D. J. Zwanenburg, and H. Wynberg, in "Deuxième Congrès Intern. de Chimie Hétérocyclique," Faculté des Sciences de Montpellier 7–11 Juillet 1969, p. III, c-7.

⁷⁹ W. B. Wright, *J. Heterocycl. Chem.* **9**, 879 (1972).

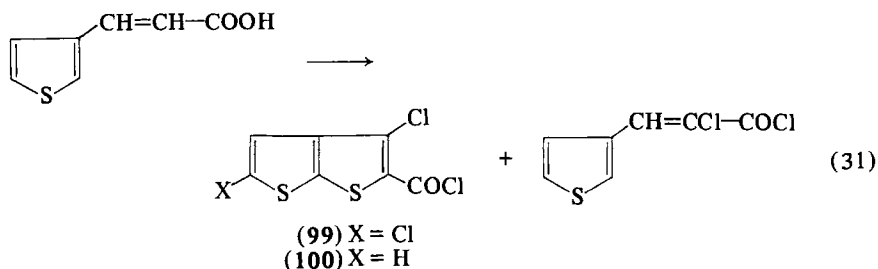
⁸⁰ A. J. Krubsack and T. Higa, *Tetrahedron Lett.*, 5149 (1968).

⁸¹ S. Nakagawa, J. Okumura, F. Sakai, H. Hoshi, and T. Naite, *Tetrahedron Lett.*, 3719 (1970).

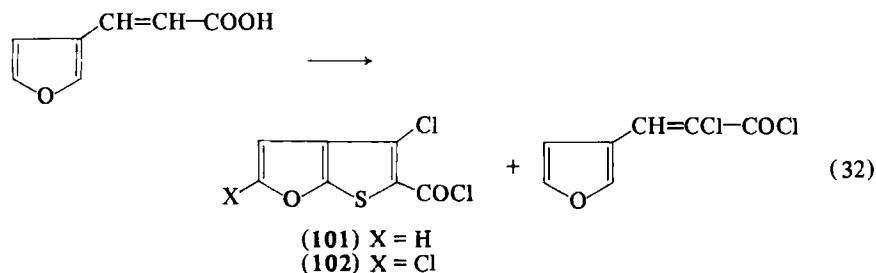
⁸² W. B. Wright and H. J. Brabander, *J. Heterocycl. Chem.* **8**, 711 (1971).

was not observed; instead, 3,5-dichlorothieno[3,2-*b*]thiophene-2-carbonyl chloride (**96**) was formed in 13% yield. A 33% yield of the latter was achieved from 3-(5-chloro-2-thienyl)acrylic acid with thionyl chloride in pyridine. 5-Bromo-3-chlorothieno[3,2-*b*]thiophene-2-carbonyl chloride (**97**) was similarly isolated (17%) from 3-(5-bromo-2-thienyl)acrylic acid, and 3-chloro-5-methylthieno[3,2-*b*]thiophene-2-carbonyl chloride (**98**) (18%) results from 3-(5-methyl-2-thienyl)acrylic acid with thionyl chloride and pyridine in toluene [Eq. (30)].

Later Gronowitz and Maltesson⁸³ reported the extension of this method to the preparation of thieno[2,3-*b*]thiophene (**1**) derivatives. A mixture of 3-(3-thienyl)acrylic acid, thionyl chloride, and pyridine was heated for 24 hours. 2-Chloro-3-(3-thienyl)-acrylic acid (4.5%), 3,5-dichlorothieno[2,3-*b*]thiophene-2-carbonyl chloride (**99**) (9.5%), 3-chlorothieno[2,3-*b*]thiophene-2-carbonyl chloride (**100**) (79.1%), and other compounds were detected by GLC among the reaction products [Eq. (31)]. Hydrolysis of the reaction mixture gave 3-chlorothieno[2,3-*b*]thiophene-2-carboxylic acid in 63% yield; dechlorination of the latter by copper in propionic acid converted it into thieno[2,3-*b*]thiophene-2-carboxylic acid.

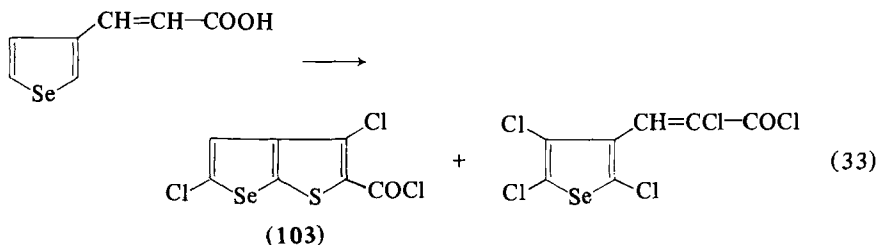


The corresponding reaction with 3-(3-furyl)acrylic acid also affords a mixture of 2-chloro-3-(3-furyl)acryloyl chloride (18%), 3-chlorothieno[2,3-*b*]furan-2-carbonyl chloride (**101**) (25%), and 3,5-dichlorothieno[2,3-*b*]furan-2-carbonyl chloride (**102**) [Eq. (32)].

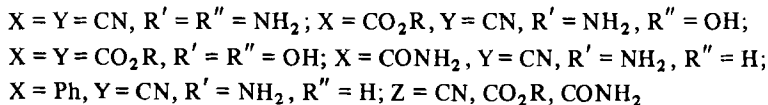
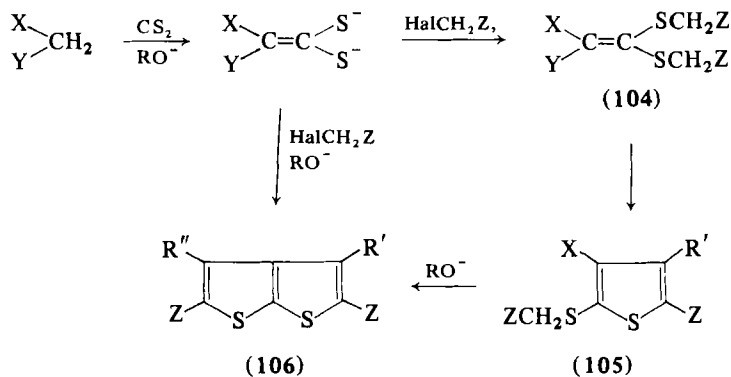


⁸³ S. Gronowitz and B. Maltesson, *Acta Chem. Scand.* 26, 2982 (1972).

Similarly, 3-(3-selenienyl)acrylic acid yields 30–40% 3,5-dichloro-selenopheno[2,3-*b*]thiophene-2-carbonyl chloride (**103**) and 15% 2-chloro-3-(2,4,5-trichloro-3-selenienyl)acryloyl chloride, together with other products [Eq. (33)]. (Experimental details for the 3-(3-furyl) and 3-(3-selenienyl)acrylic acid reactions were not given in ref. 83).



In 1962 Gompper, Kutter, and Töpfl^{84,85} prepared substituted thienothiophenes (**1**) from dithiocarboxylate salts. With haloacetic acid derivatives these give ketenemercaptals (**104**),^{86,87} which are easily converted by base into 3-amino- and 3-hydroxythiophenes (**105**). Further cyclization of **105** results in substituted thienothiophenes **106**, which may also be obtained directly by heating the dithiocarboxylates with haloacetic acid derivatives in alcoholic sodium alkoxide (Scheme 7).



SCHEME 7

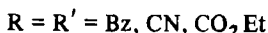
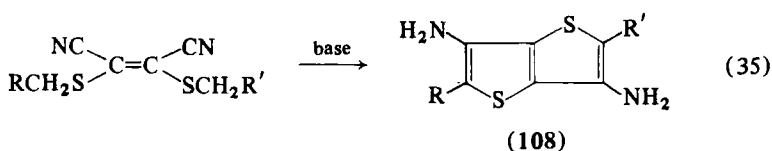
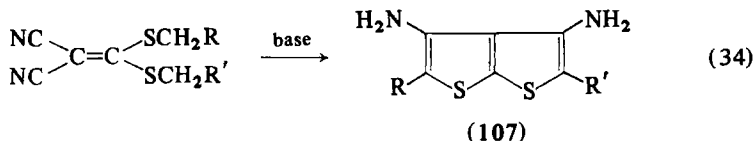
⁸⁴ R. Gompper and E. Kutter, *Angew. Chem.* **74**, 251 (1962).

⁸⁵ R. Gompper, E. Kutter, and W. Töpfl, *Ann.* **659**, 90 (1962).

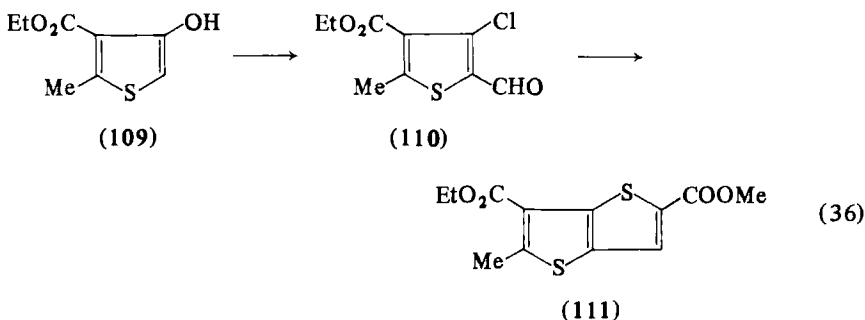
⁸⁶ R. Gompper, *Angew. Chem.* **73**, 537 (1961).

⁸⁷ W. Töpfl, *Dissertation*, T.H. Stuttgart, 1961.

Brasen,⁸⁸ independently, used a similar method to prepare substituted 3,4-diaminothiopheno[2,3-*b*]thiophenes (107) and 3,6-diaminothiopheno[3,2-*b*]thiophenes (108) [Eqs. (34) and (35)].



Substituted 3-hydroxythiophenes are convenient starting-points for the synthesis of the thieno[3,2-*b*]thiophene system. Shvedov *et al.*⁸⁹ obtained 50% of 3-chloro-3-ethoxycarbonyl-5-methylthiophene-2-aldehyde (110) from 3-ethoxycarbonyl-4-hydroxy-2-methylthiophene (109) by Vilsmeier formylation at 100°. Reaction with thioglycolic ester formed 3-ethoxycarbonyl-5-methoxycarbonyl-2-methylthieno[3,2-*b*]thiophene (111) [Eq. (36)].



To study the effect of ring strain (Mills–Nixon effect)⁹⁰ on the properties of five-membered heteroaromatics, Wynberg and Zwanenburg⁹¹ developed a new synthesis of 1*H*,3*H*-thieno[3,4-*c*]thiophene (112) [Eq. (37)]. They obtained 3,4-dimethylthiophene-2,5-dicarboxylate (113) by

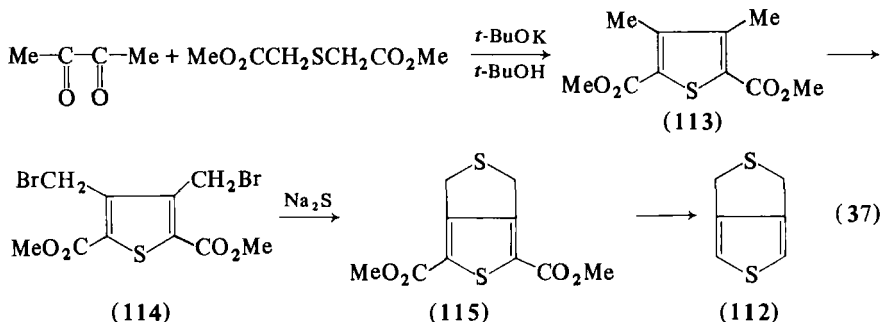
⁸⁸ W. R. Brasen, U.S. Patent 3,189,618 [CA 68, 11566c (1965)].

⁸⁹ V. I. Shvedov, V. K. Vasil'eva, and A. N. Grinev, *Khim. Geterotsikl. Soedin.*, 427 (1972).

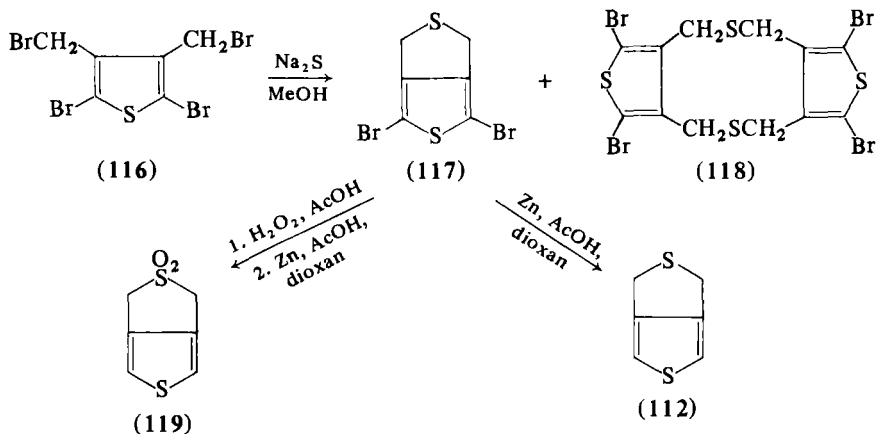
⁹⁰ W. H. Mills and J. G. Nixon, *J. Chem. Soc.*, 2510 (1930).

⁹¹ H. Wynberg and D. J. Zwanenburg, *J. Org. Chem.* 29, 1919 (1964).

the Stobbe-Johnson⁹² condensation of biacetyl with dimethylthiodiacetate. Bromination of **113** with *N*-bromosuccinimide furnished dimethyl 3,4-bisbromomethylthiophene-2,3-dicarboxylate (**114**), which with sodium sulfide gave dimethyl 1*H*,3*H*-thieno[3,4-*c*]thiophene-4,6-dicarboxylate (**115**). Saponification of **115** followed by decarboxylation produced thienothiophene (**112**).



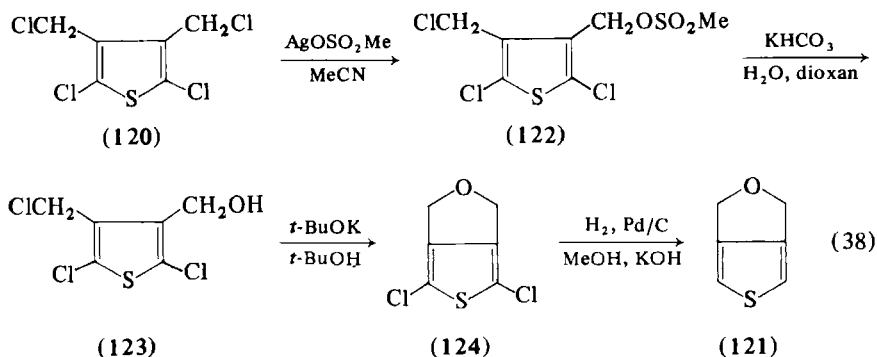
Zwanenburg and Wynberg also proposed⁹³ another route to the thienothiophene (**112**). 2,5-Dibromo-3,4-bisbromomethylthiophene (**116**) was cyclized with sodium sulfide to give 4,6-dibromo-1*H*,3*H*-thieno[3,4-*c*]thiophene (**117**) in 60% yield; **117** was then reduced to thienothiophene (**112**). 1,3,7,9-Tetrabromo-4*H*,6*H*,10*H*, 12*H*-dithieno[3,4-*c*:3',4'-*h*][1,6]dithiecin (**118**) (18%) was also formed during the ring closure. Oxidation of thienothiophene (**117**) followed by reduction by zinc in acetic acid gave 1*H*,3*H*-thieno[3,4-*c*]thiophene 2,2-dioxide (**119**).⁹³



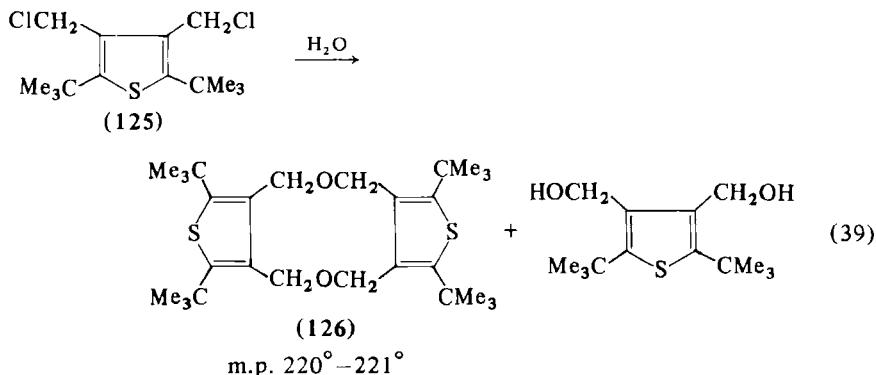
⁹² W. S. Johnson and G. H. Daub, *Org. React.* 6, 1 (1951).

⁹³ D. J. Zwanenburg and H. Wynberg, *J. Org. Chem.* 34, 333 (1969).

Zwanenburg and Wynberg⁹⁴ synthesized 1*H*,3*H*-thieno[3,4-*c*]furan (121), from 2,5-dichloro-3,4-bis(chloromethyl)thiophene (120) [Eq. (38)] with 0.5 equiv. of silver methanesulfonate in acetonitrile to give the mesylate of 2,5-dichloro-3-chloromethyl-4-hydroxymethylthiophene (122), which with KHCO_3 in aqueous dioxan yielded 2,5-dichloro-3-chloromethyl-4-hydroxymethylthiophene (123). Cyclization (KO*Bu-t*) of 123 led to 4,6-dichloro-1*H*,3*H*-thieno[3,4-*c*]furan (124) (25%), dechlorination of which over Pd/C gave the bicyclic compound 121 in 45% yield.

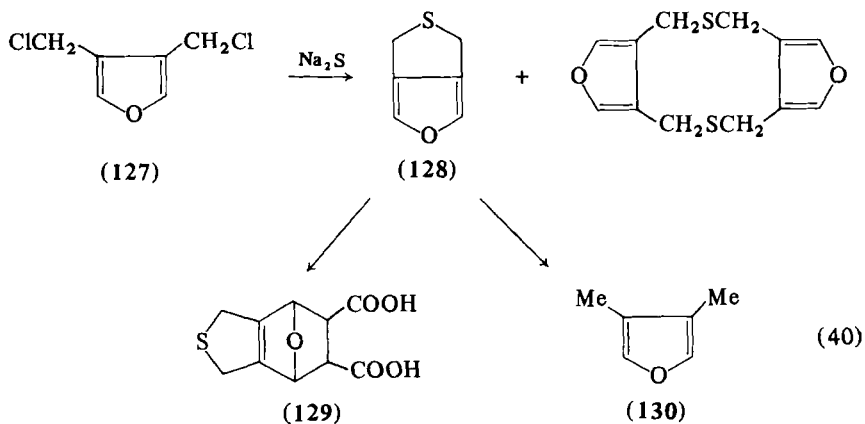


Gol'dfarb and Kondakova⁹⁵ obtained, by hydrolysis of 2,5-di-*t*-butyl-3,4-bis(chloromethyl)thiophene (125), a product with m.p. $220^\circ\text{--}221^\circ$, first thought to be 4,6-di-*t*-butyl-1*H*,3*H*-thieno[3,4-*c*]furan. However, NMR and IR spectra and molecular weight measurements demonstrated later⁹⁴ 1,3,7,9-tetra-*t*-butyl-4*H*,6*H*,10*H*,12*H*-dithieno[3,4-*c*:3',4'-*h*][1,6]-dioxecin (126) structure [Eq. (39)].

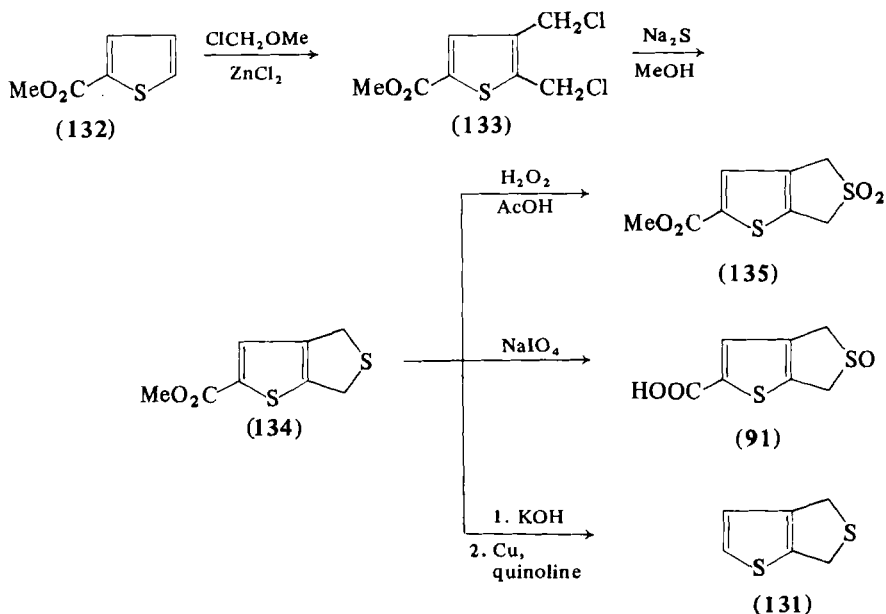


⁹⁴ D. J. Zwanenburg and H. Wynberg, *J. Org. Chem.* **34**, 340 (1969).

⁹⁵ Ya. L. Gol'dfarb and M. S. Kondakova, *Izv. Akad. Nauk SSSR, Otd. Khim. Nauk*, 1208 (1956).



Novitskii, Khachaturova and Yur'ev⁹⁶ obtained 4*H*,6*H*-thieno[3,4-*c*]-furan (128) from 3,4-bis(chloromethyl)furan (127) and sodium sulfide. The thienofuran (128) was converted into an adduct (129) with maleic anhydride and into 3,4-dimethylfuran (130) by desulfurization with Raney nickel⁹⁷ [Eq. (40)].



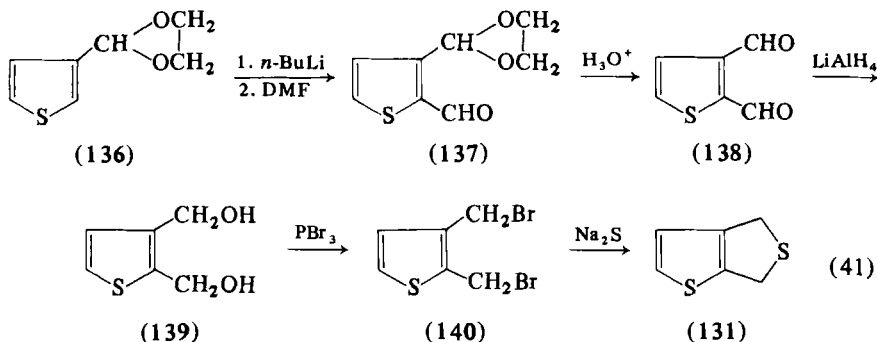
SCHEME 8

⁹⁶ K. Yu. Novitskii, G. T. Khachaturova, and Yu. K. Yur'ev, *Khim. Geterotsikl. Soedin.*, 822 (1966).

⁹⁷ K. Yu. Novitskii, G. T. Khachaturova, and Yu. K. Yur'ev, *Khim. Geterotsikl. Soedin.*, 406 (1969).

4,6-Dihydrothieno[3,4-*b*]thiophene (131) was prepared by two methods. In the first (Scheme 8), chloromethylation of methyl thiophene-2-carboxylate (132) forms methyl 2,3-bis(chloromethyl)thiophene-5-carboxylate (133) (85%); cyclization of 133 with sodium sulfide in methanol yields (66%) methyl 4,6-dihydrothieno[3,4-*b*]thiophene-2-carboxylate (134). Peroxide oxidation of 134 gives 2-methoxycarbonyl-4,6-dihydrothieno[3,4-*b*]thiophene 5,5-dioxide (135) and hydrolysis of 134 followed by metaperiodate oxidation furnishes the sulfoxide (91). Thienothiophene (131)²³ was produced by hydrolysis and decarboxylation of 134. As indicated above, the sulfoxide (91) was used for the synthesis of thieno[3,4-*b*]thiophene (3).

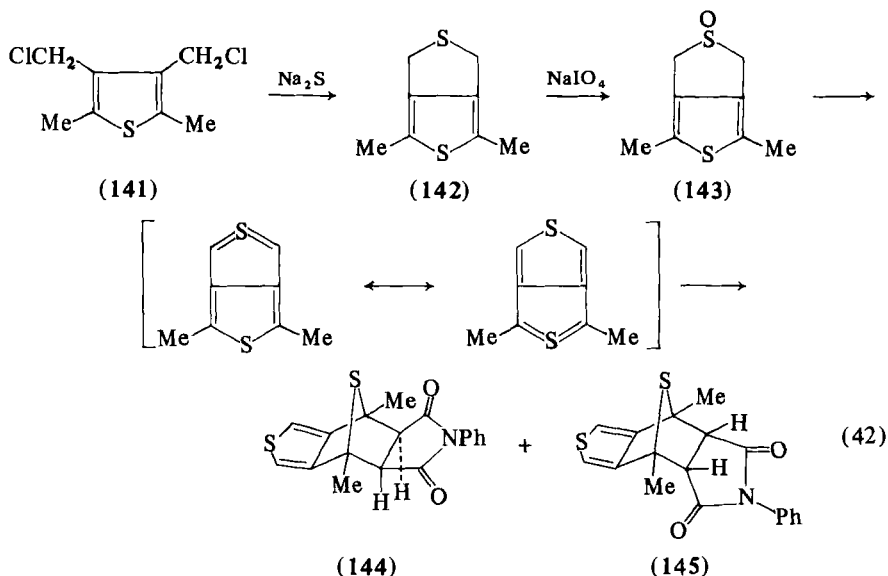
In the second route⁹⁸ to thienothiophene (131) [Eq. (41)], 3-thiophene-aldehyde ethyleneacetal (136) was converted into thiophene-2,3-dialdehyde (138), which was reduced to 2,3-bis(hydroxymethyl)thiophene (139). 139 was converted by PBr₃ into 2,3-bis(bromomethyl)thiophene (140), which with anhydrous sodium sulfide in DMF formed thienothiophene (131) (27%).



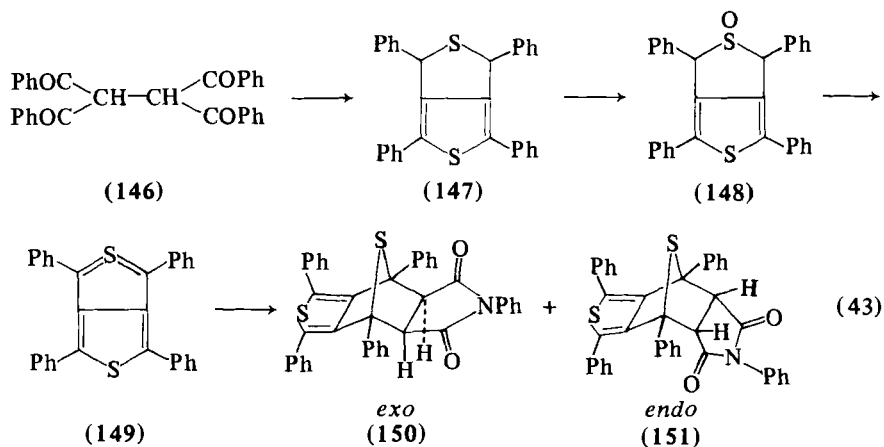
In 1967 Cava and Pollack⁹⁹ obtained derivatives of the fourth, so-called "nonclassical", thienothiophene—thieno[3,4-*c*]thiophene (4), a condensed heterocycle with formally tetravalent sulfur [Eq. (42)]. The reaction of 3,4-bis(chloromethyl)-2,5-dimethylthiophene (141) with sodium sulfide afforded 4,6-dimethyl-1*H*,3*H*-thieno[3,4-*c*]thiophene (142); periodate oxidation of 142 gave the corresponding sulfoxide (143) in 91% yield. Attempts to convert the sulfoxide (143) into the thieno[3,4-*c*]thiophene by the method used for synthesizing benzo[*c*]thiophene⁷⁶ led only to polymer. However, 24% of adduct 144 and 10% of 145 were obtained by refluxing sulfoxide (143) with *N*-phenylmaleimide in acetic anhydride, indicating that the thieno[3,4-*c*]thiophene was formed as an intermediate.

⁹⁸ D. W. H. MacDowell and T. B. Patrick, *J. Org. Chem.* **31**, 3592 (1966).

⁹⁹ M. P. Cava and N. M. Pollack, *J. Amer. Chem. Soc.* **89**, 3639 (1967).



Continuing their search for ways to synthesize this system, Cava and Husbands¹⁰⁰ allowed tetrabenzoylthane (146) to react with phosphorus pentasulfide in refluxing xylene to obtain 46% of 1,3,4,6-tetraphenyl-1*H*,3*H*-thieno[3,4-*c*]thiophene (147); oxidized with periodate the latter yielded the sulfoxide (148), which was dehydrated with acetic anhydride to produce the stable 1,3,4,6-tetraphenylthieno[3,4-*c*]thiophene (149) (87%). The latter is obtained in one step, in about 3% yield, by the reaction of tetrabenzoylthane (146) with phosphorus pentasulfide in refluxing xylene, along with the formation of 147 (30%). A mixture of two ad-



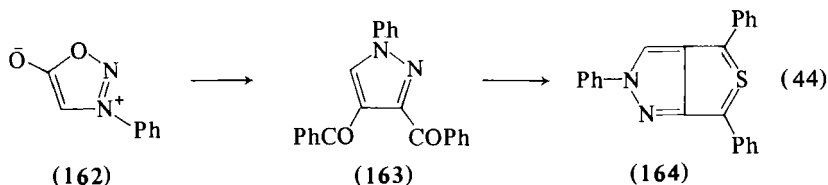
¹⁰⁰ M. P. Cava and G. E. M. Husbands, *J. Amer. Chem. Soc.* **91**, 3952 (1969).

¹⁰¹ M. P. Cava and M. A. Sprecker, *J. Amer. Chem. Soc.* **94**, 6214 (1972).

similarly, with thieno[3,4-*c*]pyrrole (159) as an intermediate. This is supported by adduct 160 formation in the reaction of the product with dimethyl acetylenedicarboxylate. The structures of the isolated adducts 157 and 160 are confirmed by mass and NMR spectroscopy and conversion into dimethyl 2,3,6,7-tetraphenylbenzo[*c*]thiophene-4,5-dicarboxylate (161).

In 1973 Cava *et al.* reported the synthesis of 4,6-dimethyl-1*H*,3*H*-thieno[3,4-*c*]thiophene (142)¹⁰² and 1,3,4,6-tetraphenylthieno[3,4-*c*]thiophene (149)¹⁰³ as well as data on some chemical conversions of the latter and the dehydration of 4,6-dimethoxycarbonyl-1*H*,3*H*-thieno[3,4-*c*]thiophene sulfoxide. Thienothiophene (149) was also obtained (42%) by Potts and McKeough¹⁰⁴ by condensation of anhydro-4-hydroxy-2,3,5-triphenylthiazolium hydroxide with dibenzoylacetylene followed by reaction of the product with P₂S₅.

Another "nonclassical" heterocycle, thieno[3,4-*c*]pyrazole, was synthesized,¹⁰⁵ utilizing the ability of mesoionic ring systems to act as 1,3 dipoles in cycloadditions.¹⁰⁶ Condensation of *N*-phenylsydnone (162) with dibenzoylacetylene formed 3,4-dibenzoyl-1-phenylpyrazole (163) (85%); with phosphorus pentasulfide in refluxing pyridine, this gave 85% of 2,4,6-triphenylthieno[3,4-*c*]pyrazole (164) [Eq. (44)]. The synthesis of 5-methyl-1,3,4,6-tetraphenylthieno[3,4-*c*]pyrrole is also described.¹⁰⁷



Oxidation (MnO₂) of thieno[2,3-*b*]thiopyrylium perchlorate gave, *inter alia*, 2-formylthieno[2,3-*b*]thiophene (12%). Similarly, thieno[3,2-*b*]thiopyrylium perchlorate afforded 2-formylthieno[3,2-*b*]thiophene (43%). When the same perchlorates were oxidized by the CrO₃-pyridine complex, the main products were 2*H*-thieno[2,3-*b*]thiopyran-2-one and 2*H*-thieno[3,2-*b*]thiopyran-2-one, respectively.¹⁰⁸

¹⁰² M. P. Cava, N. M. Pollack, and G. A. Dieterle, *J. Amer. Chem. Soc.* **95**, 2558 (1973).

¹⁰³ M. P. Cava, M. Behforouz, G. E. M. Husbands, and M. Srinivasan, *J. Amer. Chem. Soc.* **95**, 2561 (1973).

¹⁰⁴ K. T. Potts and D. McKeough, *J. Amer. Chem. Soc.* **95**, 2750 (1973).

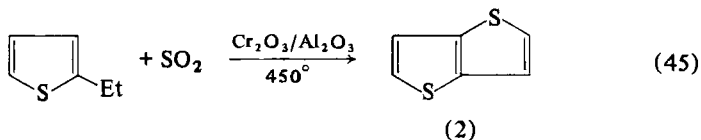
¹⁰⁵ K. T. Potts and D. McKeough, *J. Amer. Chem. Soc.* **94**, 6215 (1972).

¹⁰⁶ K. T. Potts and D. N. Roy, *Chem. Commun.*, 1061, 1062 (1968).

¹⁰⁷ K. T. Potts and D. McKeough, *J. Amer. Chem. Soc.* **95**, 2749 (1973).

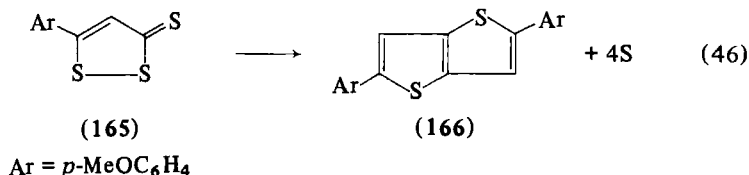
¹⁰⁸ F. Boccuzzi, J. Degani, and R. Fochi, *Ann. Chim. (Rome)* **62**, 528 (1972).

Finally, in this section of syntheses from thiophenes, a catalytic one-step method for the preparation of thieno[3,2-*b*]thiophene (2) should be mentioned. Reaction of 2-ethylthiophene with SO₂ over Cr₂O₃/Al₂O₃ at 450° afforded a 13% yield of thienothiophene 2, together with thiophene, 2-methylthiophene, 2-vinylthiophene, and 2-acetothienone^{109,110} [Eq. (45)]. Under these conditions formation of the isomeric thieno[2,3-*b*]thiophene (1) was not observed.



C. OTHER METHODS FOR SYNTHESIS OF THIENOTHIOPHENES

Böttcher and Lüttringhaus¹¹¹ thermally decomposed 5-*p*-methoxyphenyl-1,2-dithiole-3-thione (165) to obtain a small yield of a compound C₂₀H₁₆O₂S₂ assumed to be 166 [Eq. (46)].



Blazy *et al.*^{112,113} showed that addition of triethylsilane to 4- or 5-substituted 1,2-dithiole-3-thiones (167) gave compounds 168, methanolysis or pyrolysis of which produced small quantities of substituted thienothiophenes (2) [Eq. (47)].

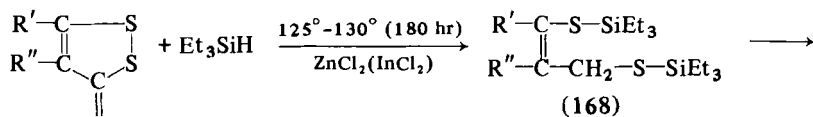
¹⁰⁹ V. P. Litvinov, E. G. Ostapenko, and Ya. L. Gol'dfarb, *Avtorsk. Svid. SSSR No. 301335* (1969); *Byull. Izobret. Tovarnykh Znakov* 14, 66 (1971).

¹¹⁰ V. P. Litvinov and E. G. Ostapenko, *Izv. Akad. Nauk SSSR, Ser. Khim.*, 1683 (1971).

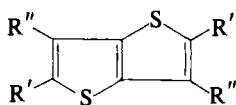
¹¹¹ B. Böttcher and A. Lüttringhaus, *Ann.* 557, 89 (1947).

¹¹² F. Blazy, J. Bonastre, and G. Pfister-Guillonzo, *Bull. Soc. Chim. Fr.*, 2136 (1966).

¹¹³ F. Blazy, J. Bonastre, and G. Pfister-Guillonzo, *Bull. Soc. Chim. Fr.*, 4247 (1968).



(167)

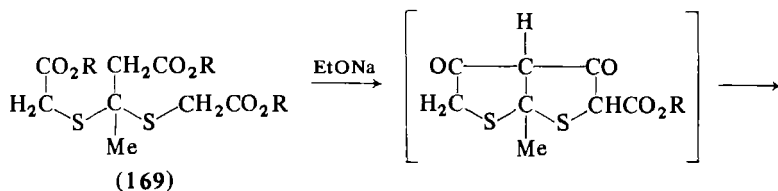


(47)

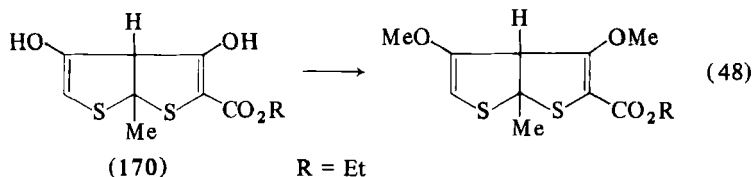
$\text{R}' = \text{Me}, \text{R}'' = \text{H}; \text{R}' = \text{Ph}, \text{R}'' = \text{H}; \text{R}' = p\text{-MeOC}_6\text{H}_4, \text{R}'' = \text{H};$

$\text{R}' = 2\text{-thienyl}, \text{R}'' = \text{H}; \text{R}' = \text{furyl}, \text{R}'' = \text{H}; \text{R}' = \text{H}, \text{R}'' = \text{Ph}$

Fiesselmann and Pfeiffer¹¹⁴ passed HCl at 0° through acetoacetic ester and thioglycolic ester in alcohol to obtain triethyl β,β -bis(carbomethoxymethylthio)butyrate (169); Dieckmann condensation reportedly furnished ethyl 3,4-dihydroxy-6a-methyl-3a,6a-dihydro-thieno[2,3-*b*]-thiophene-2-carboxylate (170) [Eq. (48)].



(169)

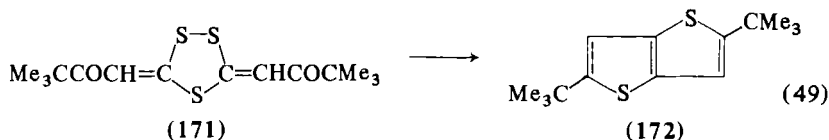


(170)

R = Et

(48)

Reduction by zinc in acetic acid of the trithiolane 171, derived from pinacolone by Gompper and Töpl,¹¹⁵ afforded 9% of 2,5-di-*t*-butyl-thieno[3,2-*b*]thiophene (172) among other products¹¹⁶ [Eq. (49)].



(171)

(172)

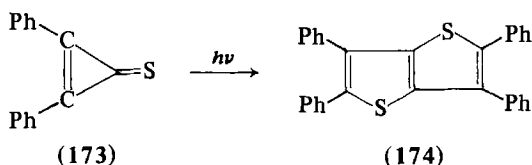
(49)

¹¹⁴ H. Fiesselmann and G. Pfeiffer, *Ber.* **87**, 848 (1954).

¹¹⁵ R. Gompper and W. Töpl, *Ber.* **95**, 2861 (1962).

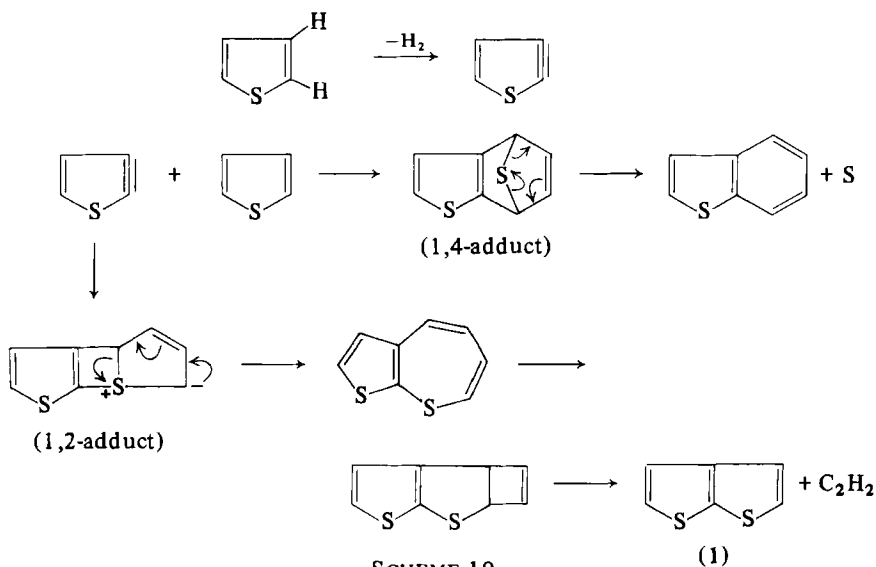
¹¹⁶ P. Yates and T. R. Lynch, *Can. J. Chem.* **49**, 1477 (1971).

Schönberg and Mamluk¹¹⁷ reported isolation of 2,3,5,6-tetraphenylthieno[3,2-*b*]thiophene (174) by exposing diphenylcyclopropenethione (173) in benzene in UV light (the yield was not mentioned).



Wynberg and Bantjes¹¹⁸ studied the pyrolysis of thiophene at 800°–850°; by mass spectrometry they established the presence of isomeric dithienyls, benzo[*b*]thiophene, and traces of naphthalene, isomeric phenylthiophenes, and thienothiophenes, besides unreacted thiophene and carbon disulfide.

In a study of the formation and reactions of arynes at high temperatures, Fields and Meyerson¹¹⁹ pyrolyzed a thiophene solution of phthalic anhydride at 690°; by mass spectrometry and gas chromatography they found benzene, naphthalene, benzo[*b*]thiophene, phenylthiophenes, bithienyls, thienothiophene 1, and naphthothiophene in the pyrolysis products. Pyrolysis of thiophene itself produced benzo[*b*]thiophene, thienothiophene 1, phenylthiophene, and bithienyl. The



SCHEME 10

¹¹⁷ A. Schönberg and M. Mamluk, *Tetrahedron Lett.*, 4993 (1971).

¹¹⁸ H. Wynberg and A. Bantjes, *J. Org. Chem.* **24**, 1421 (1959).

¹¹⁹ E. K. Fields and S. Meyerson, *Chem. Commun.*, 708 (1966).

authors assumed the formation of benzo[*b*]thiophene and thienothiophene 1 to proceed via the hetaryne "thiophyne" resulting from intramolecular pyrolytic dehydrogenation of thiophene followed by 1,4- or 1,2-addition of "thiophyne" to thiophene (Scheme 10).

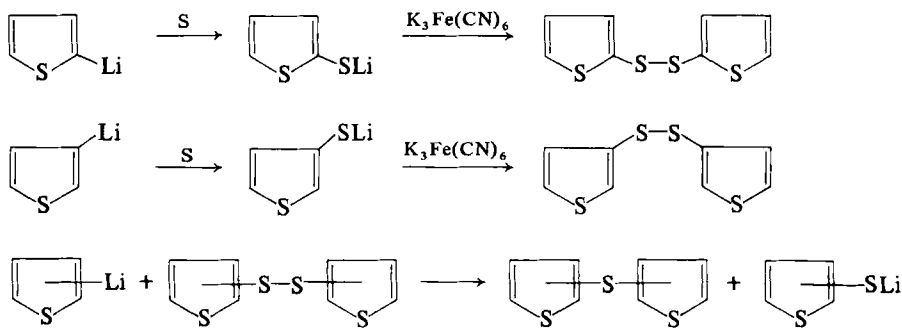
D. SYNTHESIS OF RELATED SYSTEMS

This section reviews synthetic procedures for heteroaromatic systems related to thienothiophenes, viz., dithienothiophenes, selenopheno-selenophenes, and selenophenothiophenes.

1. Synthesis of Dithienothiophenes

The first compound of this series, dithieno[2,3-*b*:3',2'-*d*]thiophene (5), was prepared as mentioned above by Pandya and Tilak,^{30,35,36} who cyclized 2,5-bis(*ω*-dimethoxyethylthio)thiophene with polyphosphoric acid.

Dithienyl sulfides have been used for the synthesis of other isomeric dithienothiophenes, the former being obtained by the method of Fyodorov and Stoyanovich¹²⁰ from thienyllithium and dithienyl disulfides. Dithienyl disulfides were prepared from thiophene or 3-bromothiophene in high yields (Scheme 11).



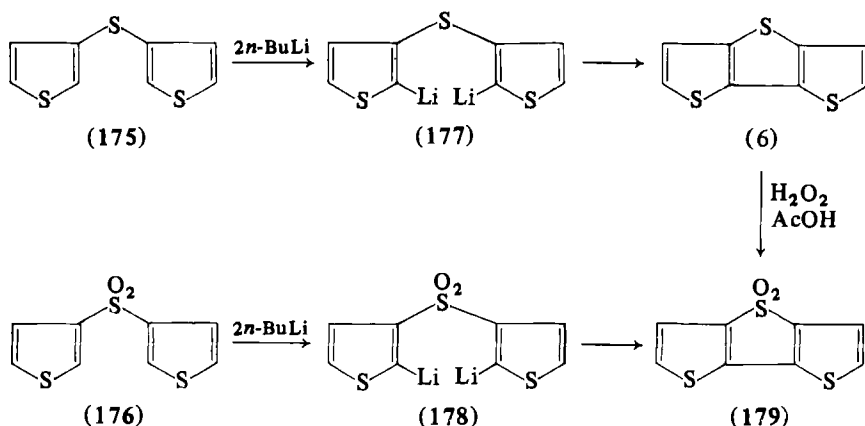
SCHEME 11

The metalation¹²⁰⁻¹²² of 3,3'-dithienyl sulfide (175) and its sulfone (176) and heating the corresponding 2,2'-dilithium derivatives (177 or 178) with cupric chloride results in dithieno[3,2-*b*:2',3'-*d*]thiophene (6) and its sulfone (179) (Scheme 12).

¹²⁰ B. P. Fyodorov and F. M. Stoyanovich, *Zh. Obshch. Khim.* 33, 2251 (1963).

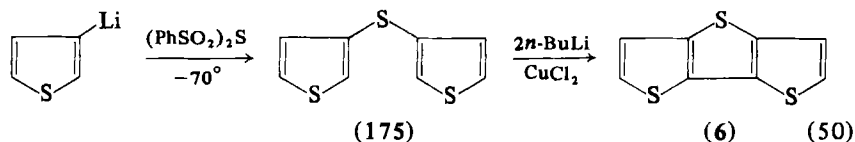
¹²¹ F. M. Stoyanovich and B. P. Fyodorov, *Zh. Org. Khim.* 1, 1282 (1965).

¹²² F. M. Stoyanovich and B. P. Fyodorov, in *Tezisy Dokladov Nauchn. Konferentsii "Geterotzykly v Organich. Sintze,"* p. 54. Kiev, 1964.

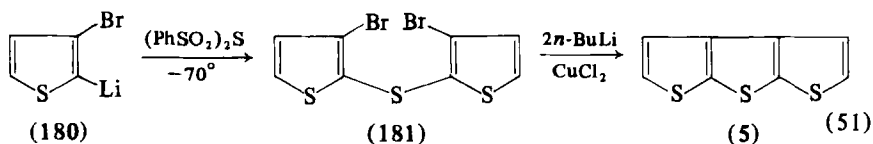


SCHEME 12

De Jong and Janssen¹²³ obtained 68% of the sulfide **175** from 3-thienyllithium and bis(phenylsulfonyl)sulfide. Dilithiation of **175** followed by oxidative ring closure¹²¹ afforded dithienothiophene **6** (52%) [Eq. (50)]. Similarly, 3-bromo-2-thienyllithium (**180**) gave 3,3'-



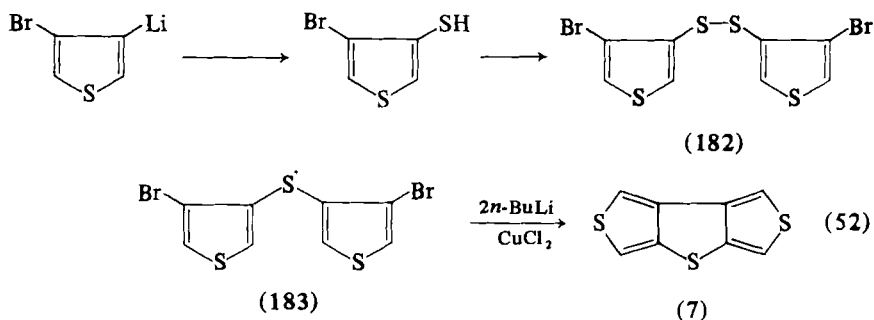
dibromo-2,2'-dithienyl sulfide (**181**), converted into dithieno[2,3-*b*:3',2'-*d*]thiophene (**5**) (21%) [Eq. (51)].



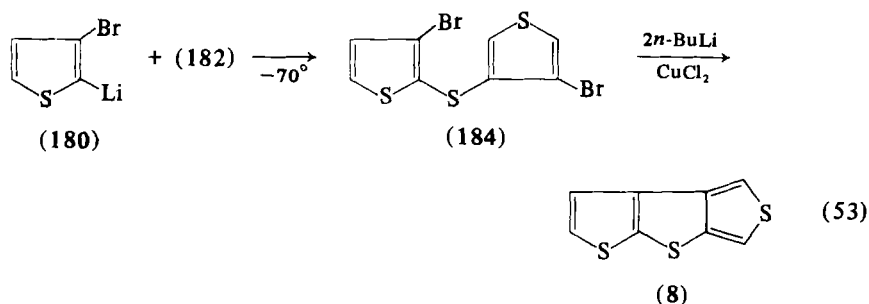
The authors^{123,124} also prepared four previously unknown isomers of dithienothiophene. Oxidation of 4-bromothiophene-3-thiol in aqueous $\text{K}_3\text{Fe}(\text{CN})_6$ gave 4,4'-dibromo-3,3'-dithienyl disulfide (**182**) (90%), and **182** with 4-bromo-3-thienyllithium formed 4,4'-dibromo-3,3'-dithienyl sulfide (**183**) (83%). Ring closure of sulfide **183** furnished dithienothiophene (**7**) (20%) [Eq. (52)].

¹²³ F. de Jong and M. J. Janssen, *J. Org. Chem.* **36**, 1645 (1971).

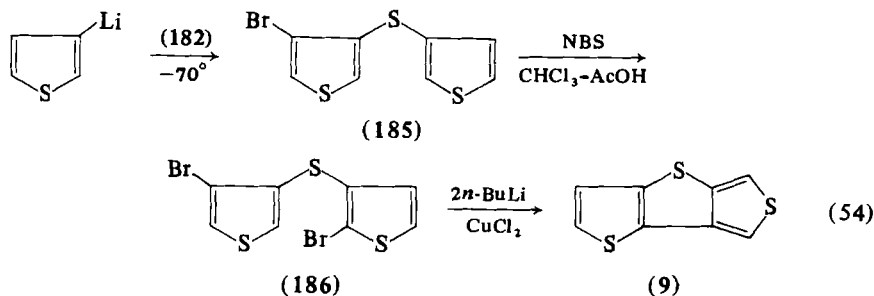
¹²⁴ F. de Jong and M. J. Janssen, *J. Org. Chem.* **36**, 1998 (1971).



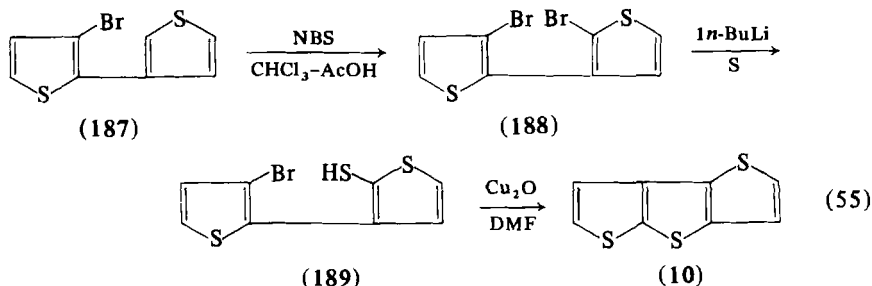
A 94% yield of 3,4'-dibromo-2,3'-dithienyl sulfide (**184**) was similarly achieved¹²⁴ from 3-bromo-2-thienyllithium (**180**) and disulfide **182**. Oxidative ring closure of the dilithium derivative of **184** gave dithienothiophene **8** in 29% yield [Eq. (53)].



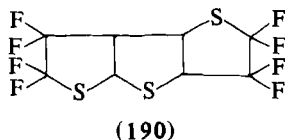
Selective bromination of monobromo-substituted dithienyl sulfides with *N*-bromosuccinimide afforded two more dithienothiophene isomers.¹²⁴ From the reaction of 3-thienyllithium with disulfide **182** at -70° , 4-bromo-3,3'-dithienyl sulfide (**185**) was isolated. Bromination with *N*-bromosuccinimide provided 2,4'-dibromo-3,3'-dithienyl sulfide (**186**); dilithiation of the latter followed by oxidative ring closure gave dithienothiophene **9** in 13% overall yield [Eq. (54)].



To synthesize the sixth dithienothiophene isomer, selective bromination of 3-bromo-2,3'-dithienyl (187) gave an almost quantitative yield of 2,3'-dibromo-3,2'-dithienyl (188).¹⁰⁴ Dithienyl 188, with butyllithium (1 equiv.) and sulfur, was converted into the unstable thiol 189, which without isolation was treated with cuprous oxide in DMF to yield 65% of dithienothiophene (10) [Eq. (55)].



Krespan^{125,126} allowed sulfur, tetrafluoroethylene, and thiophene to react at 150° to give 13% of a compound considered to be octafluoro-octahydrothieno[2,3-*b*:2',3'-*d*]thiophene (190) from elemental analysis, molecular weight measurements, and IR and NMR spectra.



2. Preparation of Selenophenoselenophenes

Systems with two condensed selenophene rings were first mentioned by Briscoe *et al.*,¹²⁷ in search of an improved synthesis of selenophene from acetylene and selenium. They obtained at 400° a mixture, including benzene, selenophene, naphthalene, and a compound, b.p. 240°–250°, containing about 20% of selenium, considered to be selenophenoselenophene (11).

Umezawa *et al.*^{128,129} analyzed the residue formed in the reaction of acetylene with selenium and isolated three selenophenoselenophene isomers: selenopheno[2,3-*b*]selenophene (11), selenopheno[3,2-*b*]selenophene (12), and selenopheno[3,4-*b*]selenophene (13). The isomers

¹²⁵ C. G. Krespan, U.S. Patent 3,119,836 [CA 60, 15834e (1964)].

¹²⁶ C. G. Krespan, *J. Org. Chem.* 27, 3588 (1962).

¹²⁷ V. A. Briscoe, J. B. Peel, and P. L. Robinson, *J. Chem. Soc.*, 2628 (1928).

¹²⁸ S. Umezawa, *Bull. Chem. Soc. Jap.* 14, 363 (1939).

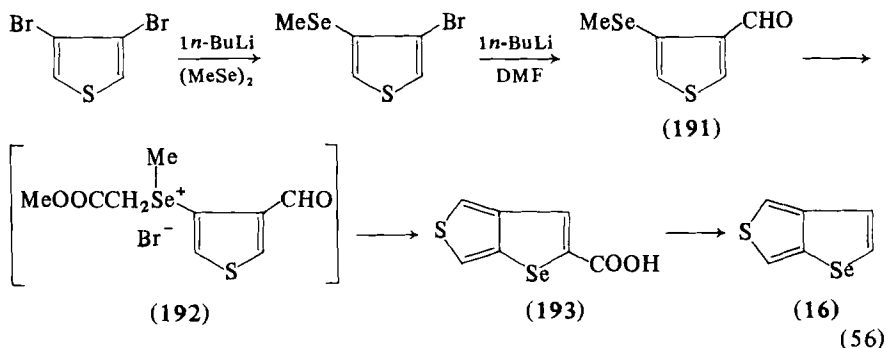
¹²⁹ B. Tamamushi, H. Akiyama, and S. Umezawa, *Bull. Chem. Soc. Jap.* 14, 318 (1939).

were separated by crystallization and distillation; the structures were assigned from dipole moments.

Apart from the above work, study of the magnetic susceptibility of selenophenoselenophenes¹³⁰ and an X-ray analysis of selenopheno-selenophene (12)¹³¹ (see below), there are no other reports on these heteroaromatic systems.

3. Preparation of Selenophenothiophenes

Heteroaromatic systems containing condensed thiophene and selenophene rings were unknown until recently. The present authors obtained selenopheno[2,3-*b*]thiophene (14) and selenopheno[3,2-*b*]thiophene (15)¹³²⁻¹³⁶ using the synthetic procedures for thienothiophenes.^{41,44,60} An attempt to isolate a third isomer, selenopheno[2,3-*c*]thiophene (16), via the route to thieno[3,4-*b*]thiophene (3),⁶³ was unsuccessful. Selenophenothiophene 16 was obtained from 4-methyl-seleno-3-thiophenealdehyde (191) and methyl bromoacetate, followed by heating the selenium salt (192) with acetic anhydride and pyridine. The acid 193 thus formed was decarboxylated to selenopheno[2,3-*c*]thiophene (16)¹³²⁻¹³⁶ [Eq. (56)].



¹³⁰ H. Tominaga, G. Hazato, and H. Oshima, *J. Chem. Soc. Jap.* **63**, 1291 (1943) [*CA* **41**, 3334d (1947)].

¹³¹ A. C. Villa, M. Nardelli, and C. Palmieri, *Acta Crystallogr., Sect. B* **25**, 1374 (1969).

¹³² Ya. L. Gol'dfarb, V. P. Litvinov, and S. A. Ozolin, *Izv. Akad. Nauk SSSR, Ser. Khim.*, 1419 (1968).

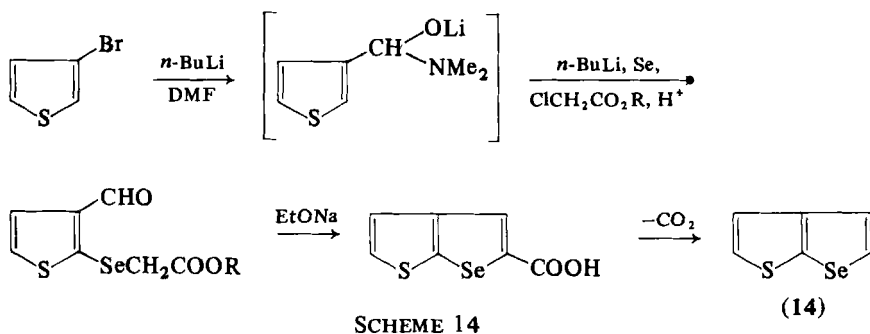
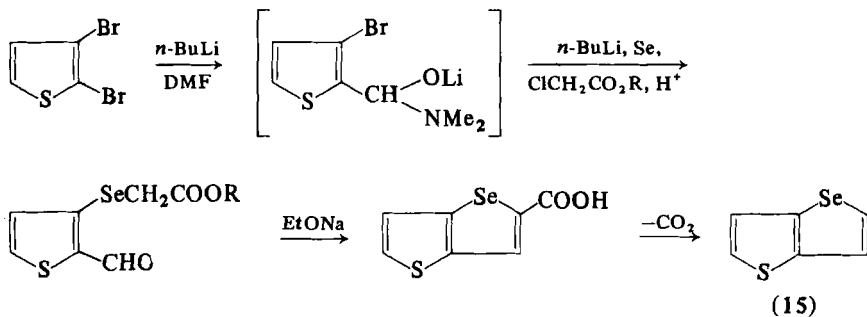
¹³³ V. P. Litvinov, A. N. Sukiasyan, and Ya. L. Gol'dfarb, in "Tezisy Dokladov XII Nauchn. Sessii po Khim. i Tekhnol. Organich. Soyed. Sery i Sernistykh Neftei," p. 119. Riga, 1971.

¹³⁴ A. N. Sukiasyan, *Dissert.*, Moscow, 1971.

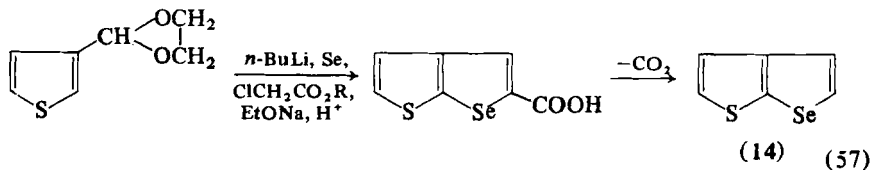
¹³⁵ V. P. Litvinov, A. N. Sukiasyan, Ya. L. Gol'dfarb, and L. V. Bogacheva, *Izv. Akad. Nauk SSSR, Ser. Khim.*, 1952 (1971).

¹³⁶ V. P. Litvinov, A. N. Sukiasyan, and Ya. L. Gol'dfarb, *Khim. Geterotsikl. Soedin.*, 723 (1972).

Litvinov *et al.*¹³⁷ prepared selenophenothiophenes 14 and 15 according to Schemes 13 and 14 by inserting two functional groups into the thiophene ring, using lithiation methods,¹³⁸ followed by intramolecular condensation of an acetic ester residue. The intermediates from the first three steps need not be isolated.



Bugge¹³⁹ synthesized selenophenothiophene 14 in a rather similar way from 3-thiophenaldehyde ethyleneacetal [Eq. (57)].



¹³⁷ V. P. Litvinov, Ya. L. Gol'dfarb, V. S. Bogdanov, I. P. Konjajeva, and A. N. Sukiasyan, *J. Prakt. Chem.* **315**, 850 (1973).

¹³⁸ U. Michael and S. Gronowitz, *Acta Chem. Scand.* **22**, 1353 (1968).

¹³⁹ A. Bugge, *Acta Chem. Scand.* **23**, 1823 (1969).

III. Molecular Structure and Physical Properties

The aromatic π -electron system of thienothiophenes and related compounds containing two condensed rings comprises electrons from three carbon-carbon double bonds and unshared electron pairs from two heteroatoms, and thus is similar to that of naphthalene.

A. STRUCTURE AND THEORETICAL CALCULATIONS

In 1949 Cox and co-workers¹⁴⁰ from X-ray structural analysis and quantum-mechanical calculations suggested that thieno[3,2-*b*]thiophene (2) possesses a ground state intermediate form between the extremes with completely localized double bonds and that with complete delocalization of π -electrons. The discrepancy between the theoretical and experimental (Fig. 1) values (0.05 Å) for the central C₇—C₈ bond was noted, and the thienothiophene (2) molecule was shown to be planar and to have a center of symmetry.

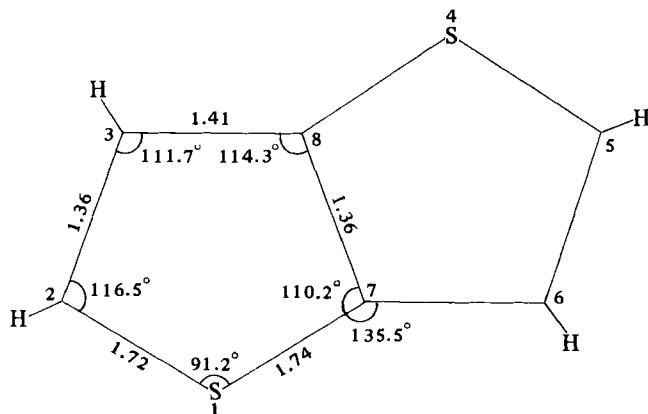


FIG. 1. Bond lengths (Å) and angles of the thieno[3,2-*b*]thiophene molecule.

Recent X-ray structural studies of selenopheno[3,2-*b*]selenophene (12)¹³¹ have shown it to be isostructural with thieno[3,2-*b*]thiophene (2). The C—C bond lengths in these molecules are nearly the same (Fig. 2).

An X-ray structural analysis of the 1,3,4,6-tetraphenylthieno[3,4-*c*]thiophene molecule (149)¹⁴¹ also has been performed (see Fig. 3).

¹⁴⁰ E. G. Cox, R. J. J. H. Gillot, and G. A. Jeffrey, *Acta Crystallogr.* **2**, 356 (1949).

¹⁴¹ M. D. Glick and R. E. Cook, *Acta Crystallogr., Sect. B* **28**, 1336 (1972).

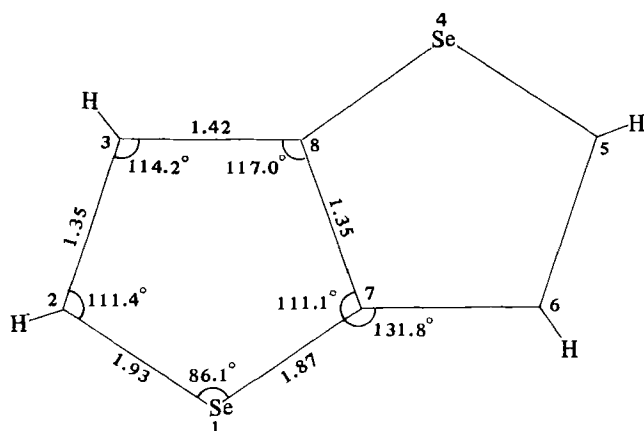


FIG. 2. Bond lengths (Å) and angles of the selenopheno[3,2-*b*]selenophene molecule.

The work of Cox *et al.*¹⁴⁰ was followed by a number of quantum calculations on thienothiophene isomers. Evans and de Heer¹⁴² calculated the bond lengths in thienothiophene 2 from bond-lengths vs. bond order relationship by an approach including sulfur 3*d* orbitals,¹⁴³

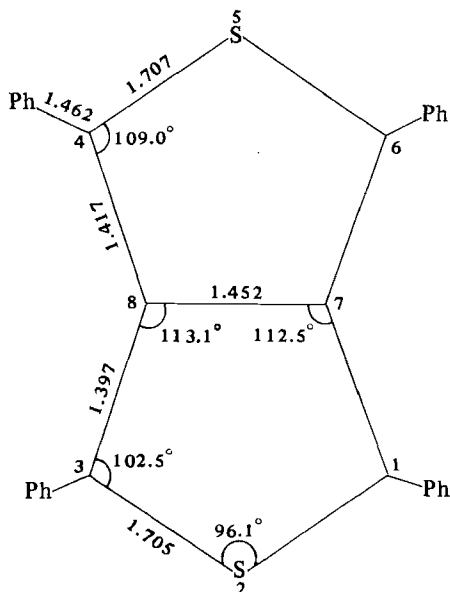


FIG. 3. Bond lengths (Å) and angles of the thienothiophene fragment of the 1,3,4,6-tetraphenylthieno[3,4-*c*]thiophene molecule.

¹⁴² M. G. Evans and J. de Heer, *Acta Crystallogr.* 2, 363 (1949).

¹⁴³ H. C. Longuet-Higgins, *Trans. Faraday Soc.* 45, 173 (1949).

used by Longuet-Higgins for thiophene. The results obtained are in accord with those given in ref. 140. The discrepancy between calculated (1.41 Å) and experimental (1.36 Å) lengths of the C_7-C_8 central bond was emphasized,^{140,143} but no explanation was given. Discrepancies in the central bond length were also observed in linear combination of atomic orbitals and molecular orbitals (LCAO MO) calculations of condensed molecules containing no heteroatoms.

In 1950 Longuet-Higgins¹⁴⁴ suggested that the shortening of C_7-C_8 central bond in thienothiophene (2) was caused by the strain of bond angles $S_1-C_7-C_6$ and $S_4-C_8-C_3$. Taking these angles to be 120° (experimental value 135.5°)¹⁴⁰ and considering the set of strains around the C_7-C_8 bond, he calculated the possible shortening of the central bond to be about 0.06 Å. This indicates a possible correlation between calculated and experimental bond lengths. Schomaker, however, showed that such bond-length shortening should not exceed 0.03 Å and should be accompanied by a shortening of the C_2-C_3 bond by 0.01 Å.¹⁴⁵

Using the self-consistent field Pariser-Parr-Pople (SCF PPP) MO method, Clark¹⁴⁶ found that calculated bond lengths, within the error limits, are in a good agreement with experiment. This was also the case with naphthalene, where Hückel calculations overestimate the length of the central C-C bond while SCF PPP calculated values are in a far better agreement with experiment.¹⁴⁷ The same method was used to calculate C-C and C-S bond lengths in the thienothiophene 2 molecule.¹⁴⁸⁻¹⁵⁰ The agreement between the calculated and experimental data is in the range of 0.002–0.016 Å, except for the C_7-C_8 central bond, where there is a discrepancy of about 0.029 Å.

Recent analysis of the bond length data in thienothiophene isomers indicates good agreement for thieno[2,3-*b*]thiophene (1) and thieno[3,2-*b*]thiophene (2). However, while the S_1-C_2 distance in thienothiophene 1 coincides exactly with S_1-C_7 distance, the calculated S_1-C_2 distance in thienothiophene 2 is somewhat shorter than S_1-C_7 . In thieno[3,4-*b*]thiophene (3) these bonds are a little longer than in thienothiophenes 1 and 2. The central C_7-C_8 bond in two condensed rings in thieno[3,4-*b*]thiophene (3) and thieno[3,4-*c*]thiophene (4) is somewhat longer than the corresponding bond in the other two isomers 1 and 2.

¹⁴⁴ H. C. Longuet-Higgins, *Acta Crystallogr.* 3, 76 (1950).

¹⁴⁵ V. Schomaker, *Acta Crystallogr.* 4, 158 (1951).

¹⁴⁶ D. T. Clark, *Tetrahedron Lett.*, 2889 (1967).

¹⁴⁷ L. Salem, in "Molecular Orbital Theory of Conjugated Systems," p. 140. Benjamin, New York, 1966.

¹⁴⁸ N. Trinajstić, *Tetrahedron Lett.*, 1529 (1968).

¹⁴⁹ T. Zivković and N. Trinajstić, *Can. J. Chem.* 47, 697 (1969).

¹⁵⁰ N. Trinajstić and A. Hinchliffe, *Croat. Chem. Acta* 39, 119 (1967).

Quantum calculations were also used to estimate reactivities¹⁵¹⁻¹⁵⁷ and to obtain theoretical electronic spectra¹⁵⁸⁻¹⁶² of thienothiophene isomers and dithienothiophenes.^{123,162}

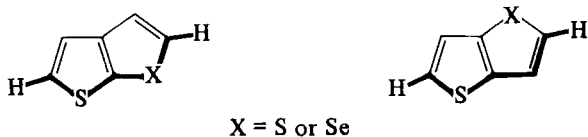
B. PROTON MAGNETIC RESONANCE SPECTRA

PMR spectroscopy has found wide application in studies of unsubstituted thienothiophenes,^{24,60,62,63,153-168} selenophenothiophenes (Table I),^{138,169} carboxy-,^{24,62,63,68,170,171} formyl-,^{68,161,164} bromo-,^{165,166,172} and alkyl-^{50,60,63,68} thienothiophenes, and carboxy-^{138,169} selenophenothiophenes. The PMR method has also been used to study alkylthieno-[3,2-*b*]thiophene sulfones^{63,162} and 4,6-dihydrothieno[3,4-*b*]thiophene (131)⁹⁸ and to analyze the mixture of products of the "thio-Claisen" rearrangement in (2-propargylthio)- (36) and (3-propargylthio)- (37) thiophenes.⁵⁰

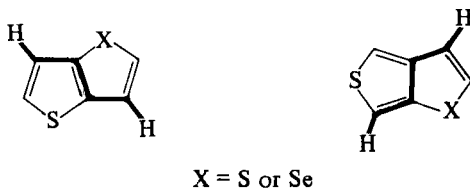
The PMR spectra of thiophene^{173,174} and selenophene^{175,176} have been thoroughly studied. The close similarity of the spin-spin coupling

- ¹⁵¹ D. T. Clark, *J. Mol. Spectrosc.* **26**, 181 (1968).
- ¹⁵² M. J. S. Dewar and N. Trinajstić, *J. Amer. Chem. Soc.* **92**, 1453 (1970).
- ¹⁵³ A. Skancke and P. N. Skancke, *Acta Chem. Scand.* **24**, 23 (1970).
- ¹⁵⁴ N. Trinajstić and Z. Majerski, *Zt. Naturforsch. A* **22**, 1475 (1967).
- ¹⁵⁵ D. T. Clark, *Tetrahedron Lett.*, 5257 (1967).
- ¹⁵⁶ D. T. Clark, *Tetrahedron* **24**, 2567 (1968).
- ¹⁵⁷ Ya. L. Gol'dfarb, V. P. Litvinov, G. M. Zhidomirov, I. A. Abronin, and R. Z. Zaharjan, *Chem. Scripta* **5**, 49 (1974).
- ¹⁵⁸ J. Fabian, A. Mehlhorn, and R. Zahradnik, *J. Phys. Chem.* **72**, 3975 (1968).
- ¹⁵⁹ R. A. W. Johnstone and S. D. Ward, *Tetrahedron* **25**, 5485 (1969).
- ¹⁶⁰ J. Fabian and H. Hartmann, *Tetrahedron Lett.*, 239 (1969).
- ¹⁶¹ A. Tajiri, T. Asano, and T. Nakajima, *Tetrahedron Lett.*, 1785 (1971).
- ¹⁶² F. de Jong and M. Janssen, *J. Chem. Soc., Perkin Trans. II*, 572 (1972).
- ¹⁶³ B. Gestblom, *Acta Chem. Scand.* **17**, 280 (1963).
- ¹⁶⁴ B. Gestblom, R. A. Hoffman, and S. Rodmar, *Acta Chem. Scand.* **18**, 1222 (1964).
- ¹⁶⁵ B. Gestblom, O. Hartmann, and A. Bugge, *J. Magnet. Reson.* **2**, 186 (1970).
- ¹⁶⁶ A. Bugge, B. Gestblom, and O. Hartmann, *Acta Chem. Scand.* **24**, 195 (1970).
- ¹⁶⁷ H. Wynberg and J. Feijen, *Rec. Trav. Chim. Pays-Bas* **89**, 77 (1970).
- ¹⁶⁸ C. A. Boicelli, A. Mangini, L. Lunazzi, and M. Tiecco, *J. Chem. Soc. Perkin Trans. II*, 599 (1972).
- ¹⁶⁹ A. Bugge, B. Gestblom, and O. Hartmann, *Acta Chem. Scand.* **24**, 1953 (1970).
- ¹⁷⁰ O. Hartmann, B. Gestblom, and A. Bugge, *Acta Chem. Scand.* **25**, 2547 (1971).
- ¹⁷¹ A. Bugge, *Acta Chem. Scand.* **22**, 63 (1968).
- ¹⁷² A. Bugge, *Acta Chem. Scand.* **23**, 2704 (1969).
- ¹⁷³ J. A. Emsley, J. Feeney, and L. H. Sutcliffe, "High Resolution Nuclear Magnetic Resonance Spectroscopy," Pergamon, Oxford, 1965.
- ¹⁷⁴ A. A. Bothner-By, *Advan. Mag. Reson.* **1**, 195 (1965).
- ¹⁷⁵ M. L. Hefferan and A. A. Humffray, *Mol. Phys.* **7**, 527 (1964).
- ¹⁷⁶ J. M. Read, C. T. Mathis, and J. H. Goldstein, *Spectrochim. Acta* **21**, 85 (1965).

constants and chemical shifts of these systems reflects the similarity in molecular structure of these heterocycles. This is also observed in thienothiophenes and selenophenothiophenes (Table I). A long-range spin-spin interaction is observed among protons in "a regular zigzag" configuration, separated by five or six bonds^{60,63,138,163,164,167-170} in thienothiophenes and selenophenothiophenes, as in other condensed heteroaromatic compounds containing sulfur, nitrogen, or oxygen as heteroatoms (see Martin-Smith¹⁷⁷ and references therein, and Takahashi *et al.*¹⁷⁸). Thus, in thieno[3,2-*b*]thiophene (2) and selenopheno[3,2-*b*]thiophene (15), long-range spin-spin coupling (~ 1.5 Hz) between protons separated by six bonds ($J_{2,5}$) is found. Similar interaction through six bonds occurs in thieno[2,3-*b*]thiophene (1) ($J_{2,5} = 1.2$ Hz) and in selenopheno[2,3-*b*]thiophene (14) ($J_{2,5} = 1.1$ Hz).



A long-range cross-ring coupling (0.7 Hz) is also found between the protons separated by five bonds in thienothiophene isomers 2 and 3, in selenopheno[3,2-*b*]thiophene (15), and selenopheno[2,3-*c*]thiophene (16).



In 2-substituted formyl thienothiophene 1 or 2 there is a slight long-range interaction ($J_{\text{CHO}-5} \sim 0.1$ Hz) between protons separated by seven bonds.¹⁷⁰ With 3-formyl thienothiophene 1 or 2 no long-range coupling is observed between the proton of the formyl group and those of the thiophene system. A similar effect is also observed in 2-methylthieno[3,2-*b*]thiophene (35) and 3-methylthieno[3,2-*b*]thiophene (27).

Selenophenothiophenes^{138,169} are also characterized by spin-spin interaction between the ⁷⁷Se isotope (spin $\frac{1}{2}$) and the protons of the selenophene fragment of the system.

¹⁷⁷ M. Martin-Smith, S. T. Reid, and S. Sternhell, *Tetrahedron Lett.*, 2393 (1965).

¹⁷⁸ K. Takahashi, J. Ito, and Y. Matsuki, *J. Chem. Soc., Jap.* 39, 2316 (1966).

TABLE
NUCLEAR PARAMETERS OF UNSUBSTITUTED

No.	Compounds	Chemical shifts (δ)			
1	Thieno[2,3- <i>b</i>]thiophene (1)	H ₂ 7.27 7.42 7.27	H ₃ 7.17 7.23 7.08	H ₄ 7.17 7.23 7.08	H ₅ 7.27 7.42 7.27
2	Thieno[3,2- <i>b</i>]thiophene (2)	H ₂ 7.52 7.48	H ₃ 7.34 7.30	H ₅ 7.52 7.48	H ₆ 7.34 7.30
3	Thieno[3,4- <i>b</i>]thiophene (3) ^a	H ₂ 7.17	H ₃ 6.74	H ₄ 7.05	H ₆ 7.15
4	Selenopheno[2,3- <i>b</i>]thiophene (14) ^b	H ₂ 7.25 7.43	H ₃ 7.11 7.25	H ₄ 7.32 7.44	H ₅ 7.71 7.93
5	Selenopheno[3,2- <i>b</i>]thiophene (15) ^c	H ₂ 7.22 7.43	H ₃ 7.14 7.35	H ₅ 7.79 8.02	H ₆ 7.35 7.52
6	Selenopheno[2,3- <i>c</i>]thiophene (16) ^d	H ₂ 7.86 7.61	H ₃ 7.16 7.02	H ₄ 7.53 7.98	H ₆ 7.42 7.60

^a Frequencies of each line in AB spectrum are given in the literature²⁴; average values of the

^b $J_{\text{Se-4}}$ 9.4; $J_{\text{Se-5}}$ 49.2; ^c $J_{\text{Se-5}}$ 47.6; $J_{\text{Se-6}}$ 7.8; ^d $J_{\text{Se-2}}$ 46.8; $J_{\text{Se-3}}$ 8.0.

Substituting a formyl, carboxy, or carbalkoxy group into a thienothiophene or selenophenothiophene molecule has no substantial effect on the coupling constants but considerably affects the chemical shifts (see Litvinov and Fraenkel⁶³ and Michael and Gronowitz¹³⁸). The chemical shifts of the protons in the selenophene ring are characteristic of different types of condensation of the thiophene and selenophene rings and increase in the order **15** > **14** > **16** irrespective of the solvent used (acetone, CCl₄).¹⁶⁹ A similar sequence is observed in the carbonyl derivatives of the isomeric selenophenothiophenes.

The chemical shifts of the α and β -protons of the thienothiophenes 1–3 are also characteristic of the different types of ring condensation and increase in a similar order: **2** > **1** > **3**.

Bugge¹⁷⁹ used PMR spectroscopy to confirm the structures of the products obtained on chlorination (*N*-chlorosuccinimide), acetylation

¹⁷⁹ A. Bugge, *Chem. Scripta* 2, 137 (1972).

I

THIENOTHIOPHENES AND SELENOPHENOTHIOPHENES

H—H		Coupling constants (Hz)					Solvent	Reference
J_{23} 5.20	J_{24} -0.02	J_{25} —	J_{34} —	J_{35} —	J_{45} 5.20	CCl ₄		60
5.23	-0.02	1.20	-0.18	-0.02	5.23	(Me) ₂ CO		160
5.25	-0.03	1.17	-0.18	-0.03	5.25	CCl ₄		168
J_{23} 5.25	J_{25} —	J_{26} —	J_{35} —	J_{36} —	J_{36} 5.25	(CD ₃) ₂ CO		63
5.25	1.55	-0.20	-0.20	0.75	5.25	(Me) ₂ CO		166
J_{23} 5.50	J_{24} —	J_{36} 0.70	J_{46} 2.50			CCl ₄		24
J_{23} 5.30	J_{25} 1.00	J_{34} —	J_{35} —	J_{45} 5.60		CCl ₄		137
5.22	1.12	-0.17	-0.06	5.66		(Me) ₂ CO		169
J_{23} 5.20	J_{25} 1.10	J_{26} —	J_{35} —	J_{36} 0.60	J_{36} 5.80	CCl ₄		137
5.21	1.49	-0.16	-0.16	0.72	5.75	(Me) ₂ CO		169
J_{23} 5.95	J_{24} —	J_{34} —	J_{36} 0.75	J_{46} 2.75		(Me) ₂ CO		137
—	—	—	0.70	2.50		CCl ₄		137

frequencies are given in this table.

(Ac₂O/SnCl₄), and nitration [Cu(NO₃)₂] of thienothiophenes 1 and 2. He recently¹⁸⁰ also studied the effect of the α -substitution (with halogen, CH₃, SCH₃, CN, NO₂, COCH₃, and COOH groups) on the chemical shifts of protons. He observed a good correlation between the shifts, reactivity constants, F (the field effect), and R (the resonance effect).¹⁸¹

C. MASS SPECTRA

Mass spectral analysis of thieno[2,3-*b*]thiophene (1) and thieno[3,2-*b*]thiophene (2)¹⁸² reveals skeletal rearrangement similar to that in

¹⁸⁰ A. Bugge, *Chem. Scripta* 3, 190 (1973).

¹⁸¹ C. G. Swain and E. C. Lupton, *J. Amer. Chem. Soc.* 90, 4328 (1968).

¹⁸² A. Bugge, *Acta Chem. Scand.* 25, 1504 (1971).

thiophene and benzo[*b*]thiophene under electron impact^{183,184} or by UV radiation.^{185,186} Mass spectra of thienothiophenes 1 and 2, although very similar, display certain differences. The spectra contain an m/e 64 fragment ($C_3H_4^{+\cdot}$), formed from the molecular ion m/e 140 by loss of CS_2 . Both thienothiophenes 1 and 2 have the m/e 76 fragment as a doublet, the ratio of $CS_2^{+\cdot}$ and $C_6H_4^{+\cdot}$ in it being 5:1. The mass spectra of thienothiophene 2 also contains m/e 102 fragment ($M-C_3H_2$) and shows a metastable transition m/e 102 \rightarrow m/e 76 ($CS_2^{+\cdot}$); these peculiarities are not found in the spectrum of thienothiophene 1. Besides, the metastable transitions from molecular ion m/e 140 to m/e 76 in isomers 1 and 2 are of different intensities.¹⁸²

The mass spectra of selenophenothiophenes 14–16 are also very similar, with the exception of small variations in peak intensities.¹³⁷ The spectra are characterized by an intense molecular ion peak m/e 188 and by identical fragmentation order, which emphasizes Se atom elimination (m/e 108).

Mass spectrometry was also used to analyze mixtures of deuterated and nondeuterated thiophenes and thienothiophenes 1 and 2,¹⁷¹ as well as to confirm the structure of 1,3,5,6-tetraphenylthieno[3,4-*c*]thiophene (149)¹⁰⁰ (see also Bugge¹⁷⁹).

D. ELECTRON SPIN RESONANCE SPECTRA

The formation of a radical-anion with a very short lifetime on the surface of a sodium–potassium alloy during the reduction of thieno[3,2-*b*]thiophene (2) at -100° was established by ESR^{187,188} (theoretical and experimental spectra are presented). The formation of the thieno[2,3-*b*]thiophene (1) radical-anion even under such extreme conditions was not observed. The difference in the stability of radical-anions of thienothiophenes 1 and 2 was accounted for by a greater degree of conjugation in thienothiophene 2 molecule as compared to 1. The spectrum of the thienothiophene 2 radical-anion distinctly exhibits two types of hydrogen atoms with coupling constants 4.87 and 0.52 Gauss. The

¹⁸³ F. de Jong, H. J. M. Sinnige, and M. J. Janssen, *Org. Mass. Spectrosc.* **3**, 1539 (1970).

¹⁸⁴ R. G. Cooks and S. L. Bernasek, *J. Amer. Chem. Soc.* **92**, 2129 (1970).

¹⁸⁵ H. Wynberg and H. van Driel, *J. Amer. Chem. Soc.* **87**, 3998 (1965).

¹⁸⁶ H. Wynberg, R. M. Kellogg, H. van Driel, and G. E. Beekhuis, *J. Amer. Chem. Soc.* **89**, 3501 (1967).

¹⁸⁷ L. Lunazzi, A. Mangini, G. F. Pedulli, and M. Tiecco, *Gazz. Chim. Ital.* **101**, 10 (1971).

¹⁸⁸ L. Lunazzi, G. Placucci, M. Tiecco, and G. Martelli, *J. Chem. Soc. B*, 1820 (1971).

higher constant was assigned to the proton nearer to the sulfur atom by analogy with ESR spectra of previously studied systems. The ratio of spin densities in the 2- and 3-positions of the thienothiophene 2 molecule is 9:1.

The reduction of thieno[3,2-*b*]thiophene-2,5-dialdehyde or dithieno-[3,2-*b*:2',3'-*d*]thiophene-2,6-dialdehyde with potassium in tetrahydrofuran or 1,2-dimethoxyethane yields the corresponding anion-radicals, the ESR of which give information on the conformation of similar carbonyl compounds.^{189,190} Cation-radicals have also been studied (see Section IV).

E. ULTRAVIOLET SPECTRA

The electronic absorption spectra of thieno[2,3-*b*]thiophene (1) and thieno[3,2-*b*]thiophene (2) were studied by Padhye and Patel both in solution and in the vapor phase.¹⁹¹ Wynberg and Zwanenburg studied thieno[3,4-*b*]thiophene (3) spectra in solution.²⁴ For thienothiophene 1, the spectrum contains a weak long-wavelength band consisting of a vibrational progression, main frequency 1250 cm⁻¹ (including bands at 298, 278.5, and 269 nm), and intense absorption at shorter wavelength (225 nm). For thienothiophene 2 there is a vibrational progression of main frequency 1238 cm⁻¹ (including bands at 278, 268.5, and 259 nm).¹⁹¹ The thienothiophene 3 spectrum consists of a medium-intensity band at 296.5 nm, another medium-intensity band consisting of a vibrational progression (275.5, 266, and 257 nm; main frequency ~ 1300 cm⁻¹), and an intense short-wavelength peak at 235 nm.²⁴

The electronic spectra of thienothiophenes 1–3 are very similar to those of their selenophenothiophene analogs (14–16) (Table II).¹³⁸ However, some differences are shown: in all cases the corresponding absorption bands in the selenophenothiophene spectra are shifted (by about 5–10 nm) to the long-wave region.

A comparison has been made of the spectra of thienothiophenes 1 and 2 with those of naphthalene and benzo[*b*]thiophene^{151,191,192} and of the spectra of 1*H*,3*H*-thieno[3,4-*c*]thiophene (112) and of 4,6-dihydro-thieno[3,4-*b*]thiophene (131) with those of thieno[*b*]- and thieno[*c*]-cycloalkenes.¹⁹³

¹⁸⁹ L. Lunazzi, G. F. Pedulli, M. Tiecco, C. Vincenzi, and C. A. Veracini, *J. Chem. Soc., Perkin Trans. II*, 751 (1972).

¹⁹⁰ M. Guerra, G. Pedulli, and M. Tiecco, *J. Chem. Soc., Perkin Trans. II*, 903 (1973).

¹⁹¹ M. R. Padhye and J. C. Patel, *J. Sci. Ind. Res., Sect. B* 15, 49 (1956).

¹⁹² J. Godart, *J. Chim. Phys.* 34, 70 (1937).

¹⁹³ D. Cagniant, P. Cagniant, and G. Merle, *Bull. Soc. Chim. Fr.*, 3828 (1968).

TABLE II

ULTRAVIOLET SPECTRA OF THIENOTHIOPHENES 1-3, SELENOPHENOTHIOPHENES 14-16, AND DITHIENOTHIOPHENES 5-10 (IN ALCOHOL)

No.	Compounds	λ_{\max} (nm)/ ϵ	Reference
1	Thieno[2,3- <i>b</i>]thiophene (1)	225 (23,600), 269 (1920), 278.5 (980), 298 (30)	191
2	Thieno[3,2- <i>b</i>]thiophene (2)	259 (12,400), 268.5 (12,100), 278 (11,000), 305 (10)	191 195
3	Thieno[3,4- <i>b</i>]thiophene (3)	235 (16,800), 257 (3370), 266 (3650), 275.5 (3650), 296.5 (5330)	24
4	Selenopheno[2,3- <i>b</i>]thiophene (14)	229 (28,400), 260 (4240), 268 (4050), 278 (3590), 288 (2500)	137
5	Selenopheno[3,2- <i>b</i>]thiophene (15)	264 (3820), 276 (4100), 287 (4450)	137
6	Selenopheno[2,3- <i>c</i>]thiophene (16)	236 (18,000), 241 (17,600), 266 (3310), 275 (2860), 303 (4400)	137
7	Dithieno[2,3- <i>b</i> :3',2'- <i>d</i>]thiophene (5)	215 (33,000), 233 (14,500), 250 (16,300)	123
8	Dithieno[3,2- <i>b</i> :2',3'- <i>d</i>]thiophene (6)	282 (19,100), 290 (25,200), 298 (17,500)	123
9	Dithieno[3,4- <i>b</i> :3',4'- <i>d</i>]thiophene (7)	255 (16,600), 278 (14,000), 290 (16,500), 310 (1000)	123
10	Dithieno[2,3- <i>b</i> :3',4'- <i>d</i>]thiophene (8)	223 (26,300), 271 (11,300), 298 (5000)	123
11	Dithieno[3;2- <i>b</i> :3',4'- <i>d</i>]thiophene (9)	223 (8900), 250 (10,500), 265 (9100), 285 (13,000), 296 (14,500), 315 (4900)	124
12	Dithieno[2,3- <i>b</i> :2',3'- <i>d</i>]thiophene (10)	253 (20,000), 266 (17,000), 278 (11,500)	124

Calculations of the UV spectra of the isomeric thienothiophenes^{147,151,158-161} indicate that, as in the case of thiophene,¹⁹⁴ 3*d* and higher sulfur orbitals hardly affect the electronic spectra of sulfur-containing condensed heteroaromatics.^{150,159,161} In the case of sulfones of thienothiophene 2 and dithienothiophenes 5-10 in which the sulfur

¹⁹⁴ M. J. Biefield and D. D. Fitts, *J. Amer. Chem. Soc.* **88**, 4804 (1966).

¹⁹⁵ "Ultraviolet Spectral Data," Amer. Petrol. Res. Inst. No. 44, Serial No. 731.

atom was assumed to form π -bonds in the sulfonyl grouping at the expense of its $3d$ orbitals, the calculations invoked the sulfur d -orbitals.¹⁶²

UV spectroscopy was used to determine the quantitative composition of a mixture of alkyl-substituted thienothiophenes 1 and 2 formed during the cyclization of 2-acetylthio-5-ethylthiophene in the presence of aluminum chloride.⁴⁰

F. INFRARED AND RAMAN SPECTRA

The IR spectrum of thieno[2,3-*b*]thiophene (1) was first reported by Godart¹⁹² in 1937 in work devoted to the UV and IR spectral analysis of thiophene, thienothiophene 1, and benzo[*b*]thiophene. Comparison of spectral features in the 4000–11,000 cm^{-1} region of thiophene and benzene, thieno[2,3-*b*]thiophene (1) and naphthalene, and benzo[*b*]thiophene, benzene, and naphthalene demonstrated, in Godart's opinion, the similarity of IR spectra (in this region) of thiophene, thienothiophene 1, and benzo[*b*]thiophene, on the one hand, and benzene, thienothiophene 1, and naphthalene, on the other hand. The molecular absorption coefficients of benzene and thiophene, as well as of naphthalene and thienothiophene 1, were also similar.

IR spectroscopy has been used for the quantitative analysis of a mixture of 5-ethyl-3-methyl-substituted thienothiophenes 1 and 2,⁴⁰ and to detect traces of thienothiophene 2 in thienothiophene 1.⁶⁰

A complete analysis of the IR spectra of thienothiophenes 1 and 2 in the gaseous, liquid, and crystalline states was carried out by Kimel'feld *et al.*^{196,197} The following isotopically substituted compounds were also studied: 2-deuterothieno[2,3-*b*]thiophene (1-2d), 2-deuterothieno[3,2-*b*]thiophene (2-2d), 2,5-dideuterothieno[2,3-*b*]thiophene (1-2,5- d_2), and 2,5-dideuterothieno[3,2-*b*]thiophene (2-2,5- d_2). The IR spectra of oriented polycrystalline films of all compounds were measured in polarized light, and Raman spectra of liquid thienothiophenes 1, 1-2d, and 1-2,5- d_2 , of crystals of thienothiophenes 2 and 2-2,5- d_2 and melts of thienothiophenes 2 and 2-2d were analyzed. The planar structure of point-group C_{2v} for thienothiophene 1 in the liquid and gaseous states was assumed. Then the thirty vibrations of compounds 1 and 1-2,5- d_2 can be divided into four symmetry classes: A_1 (11), B_1 (10), A_2 (4), and B_2 (5); the vibrations of molecule (1-2d) (C_s symmetry) are divided into two classes: A' (21) and A'' (9).

According to X-ray data,¹⁴⁰ crystalline thienothiophene 2 has inversion symmetry of position (site symmetry) C_i . The infrared data,

¹⁹⁶ Ya. M. Kimel'feld, M. A. Moskaleva, G. N. Zhizhin, V. P. Litvinov, S. A. Ozolin, and Ya. L. Gol'dfarb, *Opt. Spektrosk.* 28, 1112 (1970).

¹⁹⁷ Ya. M. Kimel'feld *et al.*, *Opt. Spektrosk.* 32, 926 (1972).

however, are better interpreted in terms of C_{2v} symmetry. Then the thirty vibrations of compounds 2 and 2-2,5-d₂ fall into four classes of symmetry: A_g (11), B_g (4), A_u (5), and B_u (10), and vibrations of thienothiophene 2-2d, having C_s symmetry, fall into two classes: A' (21) and A'' (9).

Since the IR spectrum of crystalline thienothiophene 1 shows no new bands as compared with the spectrum of its liquid state, it follows that crystal formation does not change the symmetry of the molecule. Analysis of the IR spectra of thienothiophene 2 single crystals using polarized light shows that the change in symmetry of the molecule in crystals indicated from X-ray data¹⁴⁰ is not observed in the vibrational spectrum. The spectrum of the thienothiophene 1 crystal¹⁹⁷ contains no split bands in contrast to that of thienothiophene 2,¹⁹⁶ hence, the unit cell of 1 contains only one molecule. In addition, polarization measurements indicate a distinct anisotropy of the thienothiophene 1 crystal, so the absence of splittings cannot be accounted for by the high symmetry of the crystal itself. The above considerations demonstrate that the thienothiophene 1 crystal has the C_{2v}^1 space group.

Similar results were obtained by French authors from the IR and Raman spectra of thienothiophenes 1 and 2.¹⁹⁸

G. DIPOLE MOMENTS

Dipole moments of the isomeric thienothiophenes and related systems provide significant structural data. This technique established the structures of the isomeric thienothiophenes 1–3¹⁸ and selenopheno-selenophenes 11–13.^{128,129} The dipole moments of both thieno[3,2-*b*]thiophene (2)¹⁸ and its analog, selenopheno[3,2-*b*]selenophene (12)^{128,129} are zero. Selenium substitution for one sulfur in thienothiophene 2 (or S for one Se in 12) reduces the symmetry, resulting in a dipole moment of 0.3 D for selenopheno[3,2-*b*]thiophene (15).¹³⁷ Insertion of an ethyl group into thienothiophene 2 also lowers its symmetry: the dipole moment of 2-ethylthieno[3,2-*b*]thiophene is 0.3 D³⁷. For the other pairs of isomeric thienothiophenes (1 and 3), selenophenoselenophenes (11 and 13), and selenophenothiophenes (14 and 16), the dipole moments of the [2,3-*b*] isomers are higher than those of the [3,4-*b*] isomers (Table III). The moments of 2-ethylthieno[2,3-*b*]thiophene (20) (1.54 D) and 2,5-diethylthieno[2,3-*b*]thiophene (1.55 D) have also been determined.³⁷

¹⁹⁸ Y. Cozien and P. Saumagne, *C.R. Acad. Sci., Ser. B* 276, 365 (1973).

TABLE III

DIPOLE MOMENTS OF ISOMERIC THIENOTHIOPHENES (1-3)
SELENOPHENOSELENOPHENES (11-13) AND SELENOPHENOTHIOPHENES (14-16)

Compound	Dipole moment (D)	References
Thieno[3,2- <i>b</i>]thiophene (2)	0	18
Thieno[3,4- <i>b</i>]thiophene (3) ^a	1.03	18
Thieno[2,3- <i>b</i>]thiophene (1) ^a	1.16	18
Selenopheno[3,2- <i>b</i>]selenophene (12)	0	128, 129
Selenopheno[3,4- <i>b</i>]selenophene (13)	1.07	128, 129
Selenopheno[2,3- <i>b</i>]selenophene (11)	1.52	128, 129
Selenopheno[3,2- <i>b</i>]thiophene (15)	0.3	137
Selenopheno[2,3- <i>c</i>]thiophene (16)	0.8	137
Selenopheno[2,3- <i>b</i>]thiophene (14)	1.5	137

^a Possible contamination of one isomer with the other.

H. GAS-LIQUID CHROMATOGRAPHY

To identify isomeric thienothiophenes, the chromatographic behavior of mono- and dialkyl-substituted thienothiophenes **1** and **2** was studied.¹⁹⁹⁻²⁰¹ Thienothiophene **1** and its alkylated derivatives were shown to be characterized by greater retention volumes than the corresponding thienothiophenes **2**. The linearity of the retention volume vs. boiling point relationship allowed the thienothiophene isomers to be identified. Studies on solution thermodynamics of thienothiophenes in the stationary phase showed that isomeric thienothiophenes **1** and **2** do not differ appreciably in their heats of solution. For example, the calculated heats of solution of 5-ethyl-3-methylthieno[2,3-*b*]thiophene (**26**) and 5-ethyl-3-methylthieno[3,2-*b*]thiophene (**27**) in polyethylene-glycol adipate are both about 16 kcal/mole.²⁰⁰

Chromatographic separation clarified the peculiarities of acetylthiophene cyclization in the presence of aluminum chloride.¹⁹⁹⁻²⁰¹ Gas-liquid chromatography also allowed quantitative estimates of the relative reactivities of thiophene and the isomeric thienothiophenes **1** and

¹⁹⁹ V. I. Yakerson, L. I. Lafer, F. M. Stoyanovich, V. P. Litvinov, and Ya. L. Danyushevskii, in *Tezisy Dokladov Nauchn. Konferentsii "Geterotsyклы v Organich. Sintze,"* p. 188. Kiev, 1964.

²⁰⁰ V. I. Yakerson, L. I. Lafer, and V. P. Litvinov, *Khim. Geterotsykl. Soedin.*, 672 (1965).

²⁰¹ V. I. Yakerson, L. I. Lafer, S. Z. Taits, F. M. Stoyanovitch, V. P. Litvinov, Y. L. Danyushevsky, and Ya. L. Gol'dfarb, *J. Chromatogr.* 23, 67 (1966).

2 in electrophilic substitution (formylation, acetylation, chlorination); the retention times of 3-formyl- and 3-acetyl-substituted 1 and 2 were somewhat longer than those of the corresponding 2-substituted compounds.¹⁷⁹

To characterize the relative gas-chromatographic retentions of condensed aromatics and heteroaromatics, including thienothiophenes, benzo[*b*]thiophene, dibenzothiophene, naphthobenzothiophenes, and anthrabenzo thiophenes, a system of indices, I_n , was proposed.^{202,203} In this system a series of similar linearly condensed hydrocarbons (such as benzene, naphthalene, anthracene, tetracene, pentacene, . . .) was used as a reference scale. The logarithm of the corrected retention volume (adjusted to 0°), $\log V'_z$, depends linearly upon the number of condensed benzene rings (z) in the molecule, both in the polar and nonpolar phases. I_n is expressed by Eq. (58):

$$I_n = 1000(\log V'_x - \log V'_z)/(\log V'_{z+1} - \log V'_z) + 1000 z, \quad (58)$$

where V'_x , V'_z , and V'_{z+1} are the corrected adjusted retention volumes of the substance in question (X) and of the two neighbors in the given series with $V'_z < V'_x < V'_{z+1}$. The factor 1000 is introduced because the partition coefficients of the neighbors in the series are of the order of 4–8.

Gas-liquid chromatography detects thienothiophenes in crude oil^{204,205} and coffee extract.²⁰⁶

I. OTHER PROPERTIES

Isomeric thienothiophenes, selenophenoselenophenes, and selenophenothiophenes have an odor reminiscent of naphthalene. They all show the indophenin test with isatin and concentrated sulfuric acid.

The steam-volatility of isomeric thienothiophenes allows separation from the resinous products formed during their synthesis from citric acid or acetylene. Selenophenoselenophenes are also steam-volatile.^{128,129} It is, however, very difficult to separate the isomeric thienothiophenes from each other and from benzo[*b*]thiophene with which they are also

²⁰² V. A. Ferapontov, E. G. Ostapenko, D. D. Gverdztiteli, and V. P. Litvinov, *Izv. Akad. Nauk SSSR, Ser. Khim.*, 2417 (1970).

²⁰³ D. D. Gverdztiteli, *Dissert.*, Moscow, 1970.

²⁰⁴ R. L. Hopkins, C. J. Thompson, H. J. Coleman, and H. T. Rall, *U.S. Bur. Mines, Rep. Invest. No. 6795*, 1966 [CA 65, 8619d (1966)].

²⁰⁵ H. J. Coleman, R. L. Hopkins, and C. J. Thompson, *Int. J. Sulfur Chem.*, B 6, 42 (1971).

²⁰⁶ M. Stoll, M. Winter, F. Gaustschi, J. Flament, and B. Willhalm, *Helv. Chim. Acta* 50, 628 (1967).

formed. Challenger and co-workers¹⁹ showed that fractional crystallization of styphnates and picrates is the best way of isolating and purifying the thienothiophenes obtained by the above methods. However, isomorphism is a common phenomenon among thienothiophenes, so that the melting point of a mixture of derivatives (e.g., picrates, styphnates, and mononitro-derivatives) may show no depression.^{8,18}

The reaction of thieno[2,3-*b*]thiophene (1) or thieno[3,2-*b*]thiophene (2) with an equimolar amount of bromine in glacial acetic acid gives²¹ polymer containing bromine. Thienothiophene 2 is polymerized by HBr or orthophosphoric acid in acetic acid. These polymers turn blue in sulfuric acid.^{19,22} Similar polymers are formed from thienothiophene 1; they turn red in sulfuric acid.²² Thienothiophene 1 is resinified by concentrated HCl.²⁶

Two selenophenoselenophenes, [3,2-*b*] (12) and [3,4-*b*] (13), and two selenophenothiophenes, [3,2-*b*] (15) and [2,3-*c*] (16), are crystalline and only one of each (the [2,3-*b*] isomers 11 and 14) is liquid. One thienothiophene, the [3,2-*b*] isomer (2), is solid at room temperature, forming colorless orthorhombic bipyramids from ligroin,¹⁴⁰ isomers [2,3-*b*] (1) and [3,4-*b*] (3) being liquids.

The various isomers differ considerably in stability. All three [3,2-*b*] isomers (2, 12, and 15) are stable at room temperature, as are thieno[2,3-*b*]thiophene (1) and selenopheno[2,3-*b*]selenophene (11), but the corresponding selenophenothiophene [2,3-*b*] isomer (14) slowly decomposes although it can be stored at 0°. Selenopheno[3,4-*b*]selenophene (13) and selenopheno[2,3-*c*]thiophene (16) are stable at 20°, and the analogous thieno[3,4-*b*]thiophene (3) can be stored only below -40°. ²⁴ Electron-attracting substituents greatly increase stability. Thus, thieno[3,4-*b*]thiophene-2-carboxylic acid (90) and its methyl ester are stable at 20°C.^{24,63,78} Electron donor groups have no such effect: 4,6-dimethylthieno[3,4-*b*]thiophene (88) is unstable.⁷⁵

The lability of thieno[3,4-*b*]thiophene (3) and other iso-annelated systems, such as benzo[*c*]thiophene^{207,208} and benzo[*c*]furan,²⁰⁹ may be due to the strain effect (Mills-Nixon effect;⁹⁰ see also Zwanenburg *et al.*²³ and references therein) in the condensed five-membered ring. The stability of the iso-annelated dithienothiophenes 7-9 is noteworthy.^{123,124} Simple LCAO MO method calculations on benzo[*c*]thiophene indicate²¹⁰ that its instability is due to low specific delocalization energy and high free valence index at position 1.

²⁰⁷ R. Mayer, H. Kleinert, S. Richter, and K. Gewald, *Angew. Chem.* 74, 118 (1962).

²⁰⁸ R. Mayer, H. Kleinert, S. Richter, and K. Gewald, *J. Prakt. Chem.* 20, 244 (1963).

²⁰⁹ L. F. Fieser and M. J. Haddadin, *Can. J. Chem.* 43, 1599 (1965).

²¹⁰ R. Zahradnik, C. Parkanyi, V. Horak, and J. Koutecky, *Collect. Czech. Chem. Commun.* 28, 776 (1963).

Thieno[3,4-*c*]thiophene (4) was calculated¹⁵⁵ to be 46 kcal less stable thermodynamically than thieno[3,2-*b*]thiophene (2).

The presence of benzo[*b*]thiophene in commercial naphthalene, its possible contamination with isomeric thienothiophenes 1 and 2, and their ability to poison aromatic hydrogenation catalysts led Maxted and Walker²¹¹ to develop detoxification by a preliminary short hydrogenation, in which thienothiophenes 1 and 2, and benzo[*b*]thiophene are adsorbed on the catalyst. This is followed by their hydrogenation products that can easily be oxidized with hydrogen peroxide or permolybdic acid to nontoxic sulfones; subsequent hydrogenation of the aromatic hydrocarbons is then performed as usual.

The possible presence of isomeric thienothiophenes in bituminous oils¹⁸ and in coal tar and lignite tar⁸ had quite early been suggested, without supporting data. In 1964 Dean and Whitehead²¹² suggested the presence of isomeric thienothiophenes in Agha Jari oil (Iran). In 1966, 3-methylthieno[2,3-*b*]thiophene (72) and 2-methylthieno[3,2-*b*]thiophene (35) were detected in Wasson oil, Texas.^{203,204} Thienothiophenes 1 and 2 have been found in coffee extracts by mass spectrometry and gas-liquid chromatography.²⁰⁵ Pailer *et al.*^{213,214} studied Tyrolean shale tars with high sulfur content and detected 5-ethyl-2,3,6-trimethylthieno[3,2-*b*]thiophene and an ethyltrimethylthieno[2,3-*b*]thiophene. The above are the only reports of thienothiophenes and related systems as natural products.

IV. Reactivity of Thienothiophenes

Electrophilic substitution in thieno[2,3-*b*] and [3,2-*b*]thiophene systems is expected to proceed similarly to that in thiophene (see, e.g., Gronowitz²¹⁵ and Marino²¹⁶), a substitution occurring at position 2. Schomaker and Pauling²¹⁷ were the first to discuss this effect in the case of thiophene. Challenger and Fishwick²⁶ came to a similar conclusion about thienothiophene 1 on the basis of the possible resonance forms.

²¹¹ E. B. Maxted and A. G. Walker, *J. Chem. Soc.*, 1916 (1948).

²¹² R. A. Dean and E. V. Whitehead in "6th World Petroleum Congress, 1963," Verein zur Förderung des 6. Welt-Erdöl-Kongresses, Hamburg W. Germany, Sect. 5, Paper 9, p. 261. 1964.

²¹³ M. Pailer and H. Begutter, *Monatsh.* **104**, 297 (1973).

²¹⁴ M. Pailer and H. Grünhaus, *Monatsh.* **104**, 312 (1973).

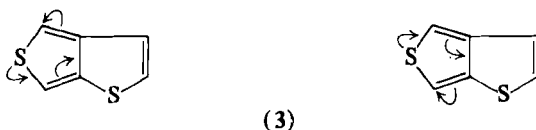
²¹⁵ S. Gronowitz, *Advan. Heterocycl. Chem.* **1**, 1 (1963).

²¹⁶ G. Marino, *Advan. Heterocycl. Chem.* **13**, 235 (1971).

²¹⁷ V. Schomaker and L. Pauling, *J. Amer. Chem. Soc.* **61**, 1769 (1939).



Thieno[3,4-*b*]thiophene (3) possesses three plausible sites of attack, positions 2, 4, and 6. However, consideration of resonance structures indicates that electrophilic substitution should occur at positions 4 or 6 rather than at 2.



The experimental data on the isomeric thienothiophenes 1–3 support these predictions. Electrophilic attack on thienothiophenes 1 and 2 results in 2-substituted compounds (see refs. 20, 21, 25, 28, 41, 218, 219). The second electrophilic substituent enters position 5. Thienothiophene 3 is attacked at positions 6 and 4 to give, for example, 4- and 6-formylthieno[3,4-*b*]thiophenes on formylation.¹⁶⁷

Lithiation by hydrogen abstraction by *n*-butyllithium in the isomeric thienothiophenes 1–3 proceeds by a different mechanism, but again results in 2-substitution in thienothiophenes 1 and 2^{41,171,220} and 4- and 6-substitution in thienothiophene 3.¹⁶⁷

There are no experimental data on the reactivity of thieno[3,4-*c*]thiophene (4) except some indications of the ease of addition reactions of its alkyl- and phenyl-substituted derivatives.^{99,100} There are no reports of the reactions of the isomeric selenophenoselenophenes, selenophenothiophenes, and dithienothiophenes, except on the oxidation of the last.^{118,119}

A. ISOTOPE EXCHANGE OF DEUTERATED THIENOTHIOPHENES: QUANTUM-CHEMICAL REACTIVITY CALCULATIONS

The first quantitative data comparing the reactivities of the α -positions in isomeric thienothiophenes 1 and 2 with that of thiophene appeared in 1970.²¹⁹ The kinetics of electrophilic dedeuteriation of the

²¹⁸ F. Challenger and G. M. Gibson, *J. Chem. Soc.*, 305 (1940).

²¹⁹ T. A. Yakushina, E. N. Zvyagintzeva, V. P. Litvinov, S. A. Ozolin, Ya. L. Gol'dfarb, and A. I. Shatenshtein, *Zh. Obshch. Khim.* **40**, 1622 (1970).

²²⁰ Ya. L. Gol'dfarb, S. A. Ozolin, and V. P. Litvinov, *Zh. Obshch. Khim.* **37**, 2220 (1967).

following compounds was measured: 2-deuterothieno[2,3-*b*]thiophene (1-2d), 2-deuterothieno[3,2-*b*]thiophene (2-2d), 2,5-dideuterothieno[2,3-*b*]thiophene (1-2,5-d₂), 2,5-dideuterothieno[3,2-*b*]thiophene (2-2,5-d₂), 3,4-dideutero-2,5-diethylthieno[2,3-*b*]thiophene, 3,6-dideutero-2,5-diethylthieno[3,2-*b*]thiophene, 2-deuterobenzo[*b*]thiophene, and 3-deuterobenzo[*b*]thiophene with acid (CF₃COOH in MeCOOH or CCl₄). The results (Table IV) indicate that the rate of electrophilic deuterium-hydrogen exchange at the α -position in thienothiophenes is greater than

TABLE IV

DEDEUTERATION RATE CONSTANTS FOR THIENOTHIOPHENES 1 AND 2 AND
BENZO[*b*]THIOPHENE AT 25°

Compound	k (sec ⁻¹)	k_{relative}^a
2-Deuterothieno[2,3- <i>b</i>]thiophene	$(4.4 \pm 0.3) \times 10^{-5}$	$k:k$ of α -position in thiophene = 7.8
2,5-Dideuterothieno[2,3- <i>b</i>]thiophene	$(5.1 \pm 0.1) \times 10^{-5}$	
2-Deuterothieno[3,2- <i>b</i>]thiophene	$(4.0 \pm 0.2) \times 10^{-5}$	$k:k$ of α -position in thiophene = 7.1
2,5-Dideuterothieno[3,2- <i>b</i>]thiophene	$(4.5 \pm 0.1) \times 10^{-5}$	
2,5-Diethyl-3,4-dideuterothieno[2,3- <i>b</i>]thiophene	$(2.2 \pm 0.1) \times 10^{-5}$	$k:k$ of β -position in 2,5-diethylthiophene = 1.4
2,5-Diethyl-3,6-dideuterothieno[3,2- <i>b</i>]thiophene	$(5.2 \pm 0.4) \times 10^{-6}$	$k:k$ of β -position in 2,5-diethylthiophene = 0.3
2-Deuterobenzo[<i>b</i>]thiophene	$(1.3 \pm 0.1) \times 10^{-8}$	$k:k$ of α -position in thiophene = 0.002
3-Deuterobenzo[<i>b</i>]thiophene	$(2.1 \pm 0.3) \times 10^{-8}$	$k:k$ of β -position in thiophene = 10

^a Deuterium exchange rate constants at α - and β -positions in thiophene are 6×10^{-6} and 2×10^{-9} sec⁻¹, respectively^{223,224}; at the β -positions in 2,5-diethylthiophene the rate constant is 1.6×10^{-5} sec⁻¹.

in thiophene, irrespective of the condensation type. In the corresponding condensed benzene system the reactivity increase is much sharper: the ratio of the rate for the α - and β -positions of naphthalene and that for benzene at 25°, is 1079 and 127, respectively, in a system containing 95.31% CF₃COOH, 2.21% H₂O, 2.48% H₂SO₄,²²¹ and 50,000 and 1200, respectively, in liquid HBr.²²²

²²¹ C. Eaborn and R. Taylor, *J. Chem. Soc.*, 1012 (1961).

²²² E. N. Yurygina, P. P. Alikhanov, E. A. Izrailevich, P. N. Manochkina, and A. I. Shatenshtein, *Zh. Fiz. Khim.* **34**, 587 (1960).

Insertion of electron-donor ethyl groups into both α -positions in thiophene raises the β -atom exchange rate by almost four orders of magnitude (1.6×10^{-5} and 2×10^{-9} sec $^{-1}$).^{223,224} The strong activating effect of alkyl groups also occurs in the isomeric thienothiophenes 1 and 2 where the β exchange rate approaches that of the α in unsubstituted compounds. There is, however, some difference between 3,4-dideutero-2,5-diethylthieno[2,3-*b*]thiophene and 3,6-dideutero-2,5-diethylthieno[3,2-*b*]thiophene: the exchange reaction rate of the former is four times greater than that of the latter, with β -atom exchange rate constants in 2,5-diethylthieno[2,3-*b*]thiophene and 2,5-diethylthiophene being about equal (2.2×10^{-5} and 1.6×10^{-5} sec $^{-1}$).

The reactivity of the thiophene ring is significantly altered by annelation in benzo[*b*]thiophene. Electrophilic hydrogen exchange occurs^{1,225} preferentially as position 3, but also furnishes appreciable amounts of the 2-isomer. In contrast to thiophene, in which α exchange with acid is much faster than β (6×10^{-6} and 2×10^{-9} sec $^{-1}$), the reactivities of the thiophene ring α - and β -positions in benzo[*b*]thiophene are almost equal (1.3×10^{-8} sec $^{-1}$). This is the result of a sharp decrease of the α exchange rate and some increase of the β rate. Eaborn and Sperry had earlier²²⁶ reported that hydrogen exchange at the thiophene α -position was sharply decreased by benzo-fusion while the β -position was little deactivated. Partial rate factors are, for the α -position in thiophene, 4810, and for positions 2 and 3 in benzo[*b*]thiophene, 39.6 and 40.7, respectively. Similar results have been noted by other authors.²¹⁹

Recently Bugge¹⁷⁹ studied the reactivities of thienothiophenes 1 and 2 and thiophene by the competitive method, utilizing SnCl $_4$ -catalyzed acetylation with acetic anhydride, Vilsmeier formylation and chlorination with *N*-chlorosuccinimide. Thienothiophenes 1 and 2 are always more reactive than thiophene. In acetylation the reactivities of 1 and 2 are similar, while in formylation and chlorination thienothiophene 2 is somewhat more reactive than isomer 1 (Table V).

Bugge calculated relative rates of various electrophilic substitutions with respect to the β -position in thiophene (Table VI). The following order of decreasing reactivity applied: α -position in thienothiophene 2 \approx α -position in thienothiophene 1 > α -position in thiophene > β -position in thienothiophene 1 \geq β -position in thienothiophene 2 > β -position in thiophene.

²²³ E. N. Zvyagintzeva, T. A. Yakushina, and A. I. Shatenshtein, *Zh. Obshch. Khim.* **38**, 1993 (1968).

²²⁴ E. N. Zvyagintzeva, L. I. Belenkii, T. A. Yakushina, Ya. L. Gol'dfarb, and A. I. Shatenstein, *Zh. Obshch. Khim.* **38**, 2004 (1968).

²²⁵ B. Iddon and R. M. Scowston, *Advan. Heterocycl. Chem.* **12**, 177 (1970).

²²⁶ C. Eaborn and J. A. Sperry, *J. Chem. Soc.*, 4921 (1961).

TABLE V

THE REACTIVITIES OF THIENOTHIOPHENES 1 AND 2 RELATIVE TO THIOPHENE^a

Reaction	1: $k/k_{\text{thiophene}}$	2: $k/k_{\text{thiophene}}$
Acetylation	3.17	2.97
Formylation	34.0	44.4
Chlorination	23.9	33.2

^aFrom Bugge¹⁷⁹ with permission of the Royal Swedish Academy of Sciences.

Italian authors²²⁷ found the following order of decreasing reactivity in halogenation and acylation: α -position in thiophene > β -position in benzo[*b*]thiophene > α -position in benzo[*b*]thiophene > β -position in thiophene.

The rates of base-catalyzed (protophilic) deuterium exchange of thiophene and thienothiophenes 1 and 2 in *t*-butanol or DMS have been determined.²²⁸ The rates of exchange at position 2 in the isomeric thienothiophenes at 25° are practically identical and 9–10 times greater than those in thiophene. Deuterium exchange at position 2 was found for all the compounds studied to be substantially greater than at position 3. Protophilic hydrogen exchange and metalation proceed in a similar way²²⁹; *n*-butyllithium metalation of the thienothiophenes 1 and 2,^{41,171,220} thiophene,²²⁷ and benzo[*b*]thiophene,²²⁵ proceeds via hydrogen substitution for a metal at position 2. By competition experiments, thienothiophenes 1 and 2 were shown¹⁷¹ to be 6.2 and 5.8

TABLE VI

PARTIAL RELATIVE RATES^a

Reaction	Thiophene		Thieno[2,3- <i>b</i>]thiophene (1)		Thieno[3,2- <i>b</i>]thiophene (2)	
	β	α	α	β	α	β
Acetylation	1	200	628	6.3	589	4.8
Formylation	1	>10 ³	>3.39 × 10 ⁴	≥68.0	>4.44 × 10 ⁴	ND ^b
Chlorination	1	250	5.95 × 10 ³	23.9	8.29 × 10 ³	<8.3

^aFrom Bugge¹⁷⁹ with permission of the Royal Swedish Academy of Sciences.^bND, not determined.²²⁷ S. Clementi, P. Linda, and G. Marino, *J. Chem. Soc.*, 79 (1971).²²⁸ T. A. Yakushina, I. O. Shapiro, E. N. Zvyagintzeva, V. P. Litvinov, S. A. Ozolin, Ya. L. Gol'dfarb, and A. I. Shatenstein, *Zh. Obshch. Khim.* 41, 1930 (1971).²²⁹ A. I. Shatenshtein, in "Isotopnii Obmen i Zameshchenie Vodoroda v Organich. Soyed," p. 107. Izd. Akad. Nauk SSSR, Moscow, 1960.

times more reactive than thiophene (cf. the deuterium exchange rate factors of 9–10²²⁸ in Table VII). The comparison of relative deuterium exchange rates (*f*) in hydrogen exchange in base²²⁸ and acid²¹⁹ in the case of benzo[*b*]thiophene showed some increase in protophilic exchange rate and a considerable slowing-down of the electrophilic exchange, produced by benzo-fusion. This is in contrast to the thienothiophenes 1

TABLE VII

RELATIVE HYDROGEN EXCHANGE RATES WITH BASES AND ACIDS

Compound	Position 2		Position 3	
	Base	Acid	Base	Acid
Thiophene	1	1	1	1
Thieno[2,3- <i>b</i>]thiophene (1)	10	8	90	—
Thieno[3,2- <i>b</i>]thiophene (2)	9	7	10 ⁴	—
Benzo[<i>b</i>]thiophene	4	0.002	65	10

and 2, in which the rates of exchange at position 2 is but little increased compared with that in thiophene, irrespective of the reaction mechanism (Table VII).

Because of the instability of thienothiophenes 1 and 2 to acids stronger than trifluoroacetic, quantitative rates for electrophilic hydrogen exchange at position 3 in these systems are not available. The rates of the acid- and base-catalyzed exchange reactions of benzo[*b*]thiophene at position 3 are greater than in thiophene. The reactivities of positions 2 and 3 in benzo[*b*]thiophene in the reaction with base differ greatly (*f* values are 4 and $\sim 10^{-4}$),²²⁸ while in the reaction with acid the reactivities are almost identical ($k = 1.3 \times 10^{-8}$ and $2.1 \times 10^{-8} \text{ sec}^{-1}$).²¹⁹ The protophilic exchange reaction involves carbanion formation; the stabilization of the carbanion formed by proton detachment from position 2 is greatly favored by conjugation with vacant 3*d* orbitals of the sulfur atom.²³⁰ The same effect is observed at position 2 in thiophene and thienothiophenes 1 and 2. Therefore in these cases the condensation type (with a thiophene or benzene ring) is of secondary importance. The rate ratios for protophilic deuterium exchange at position 2 in thiophene, thienothiophenes 1 and 2 and benzo[*b*]thiophene is 1:10:9:4. Ring annelation is of great importance in the electrophilic substitution reaction, which is characterized by the absence of *d*-orbital conjugation

²³⁰ A. I. Shatenstein, A. G. Kamrad, I. O. Shapiro, Yu. I. Raneeva, and E. N. Zvyagintzeva, *Dokl. Akad. Nauk SSSR* 168, 364 (1966).

effect and the presence of possible p,π -conjugation involving an electron pair of the second sulfur atom. The ratio of rate constants in this case is 1:8:7:0.002, respectively. The electron density near the carbon atom at position 2 in thienothiophene isomers 1 and 2 is somewhat increased at the expense of an electron pair from the second sulfur atom, and the rate of electrophilic substitution correspondingly increases. In the case of benzo[*b*]thiophene, this effect does not exist. Moreover, electron-donor p,π -conjugation to the 2-position, possible in the thiophene molecule, is less important in benzo[*b*]thiophene. This may provide an explanation for the much slower electrophilic exchange at position 2 of benzo[*b*]thiophene as compared with thiophene ($f = 0.002$).

The data on the protophilic exchange at position 3 show the reaction in the condensed heteroaromatics to proceed faster than in thiophene, irrespective of the type of ring fusion. A similar phenomenon is observed for protophilic exchange reactions in naphthalene as compared with benzene.²²² The two orders of magnitude difference between the rate constants of hydrogen exchange at position 3 of thienothiophenes 1 and 2 is somewhat unexpected. The considerably greater rate for thienothiophene 2 may be due to coordination of the potassium ion of the catalyst by the sulfur atom of one of the rings favoring subsequent butoxide attack on the deuterium atom at position 3 in the second ring.

Aromatic substitution reactions are often complicated and multistep processes. A correlation, however, in many cases can be found between the charged attacking species and the electron density distribution in the molecule attacked during electrophilic and nucleophilic substitution. No such correlation is expected in radical substitution where the attacking particles are neutral, rather a correlation between the reactivities of separate bonds and a free valency index of the bond order. This allows the prediction of the most reactive bonds. Such an approach has been used by researchers who applied quantum calculations to estimate the reactivities of the isomeric thienothiophenes and to compare them with thiophene or naphthalene.¹⁵¹⁻¹⁵⁷ Until recently quantum methods for studying reactivities of aromatics and heteroaromatics were developed mainly in the π -electron approximation (see, for example, Streitwieser²³¹ and Zahradnik^{232,233}). The 3*d* orbitals of a sulfur atom were shown not to contribute substantially to calculations of dipole moments,²³⁴ polarographic reduction potentials,²³⁵ spin-density distribution,^{236,237}

²²¹ A. Streitwieser, "Molecular Orbital Theory for Organic Chemists." Wiley, New York, 1961.

²²² R. Zahradnik, *Advan. Heterocycl. Chem.* **5**, 1 (1965).

²²³ R. Zahradnik, *Int. J. Sulfur Chem.* **B 6**, 142 (1971).

²²⁴ H. Lumbroso and R. Passerini, *Bull. Soc. Chim. Fr.*, 311 (1957).

²²⁵ K. Boček, A. Mangini, and R. Zahradnik, *J. Chem. Soc.*, 255 (1963).

²²⁶ R. Gerdil and E. A. C. Lucken, *J. Amer. Chem. Soc.* **87**, 213 (1965).

²²⁷ L. Lunnazzi, G. Placucci, and M. Tiecco, *Tetrahedron Lett.*, 3847 (1972).

electronic spectra,^{151,194,238} etc. To estimate reactivity, a great number of indices have been proposed, the localization energy being the most adequate and convenient.

Semiempirical methods of calculation with consideration of all valence electrons have been used only recently but already have given results on the reactivities of some aromatic and heteroaromatic compounds.^{157,239-243} Thus, to analyze the reactivities of thiophene and the isomeric thienothiophenes 1-3 to electrophilic substitution,¹⁵⁷ the semiempirical SCF LCAO MO method CNDO/2 was used, taking into account all valence electrons.²⁴⁴ The 3s, 3p, and 3d orbitals have been taken into account for the sulfur atom.²⁴⁵ The reactivities were estimated from the difference between bond energies of the initial and the protonated molecule (in σ complex).¹⁵⁷

The following order of positional reactivities in thiophene and the isomeric thienothiophenes (1-3) in electrophilic substitution was proposed: $C_4(3) > C_6(3) > C_2(2) > C_2(1) > C_2(3) > C_2$ (thiophene) $> C_3(3) > C_3(1) > C_3(2) > C_3$ (thiophene). This agrees with that experimentally derived on thienothiophenes 1 and 2 and thiophene¹⁷⁹: $C_2(2) > C_2(1) > C_2$ (thiophene) $> C_3(1) > C_3(2) > C_3$ (thiophene), and with the fact that in the Vilsmeier formylation position 4 in thienothiophene 3 is more reactive than position 6.¹⁶⁷

The reactivities of isomeric thienothiophenes calculated in π -electron approximation by the PPP method,¹⁵⁶ and those calculated considering all valence electrons,¹⁵⁷ show reasonable agreement. It should be noted, however, that the choice of parameters in PPP calculations is somewhat arbitrary, especially for heavy atoms (e.g., sulfur). This may lead to a discrepancy between theoretical (in π -electron approximation) and experimental estimation of reactivities. For example, Clark¹⁵⁶ applied the semiempirical method PPP SCF MO to calculate the reactivities of different positions in thienothiophenes 1-3, thiophene, and naphthalene from the localization energy values and found the following order of decreasing reactivity for electrophilic substitution: thieno[3,4-*b*]-thiophene (3) $>$ thieno[2,3-*b*]-thiophene (1) $>$ thieno[3,2-*b*]-thiophene (2) $>$ thiophene; for nucleophilic substitution: thieno[3,4-*b*]-thiophene (3) $>$ thieno[3,2-*b*]-thiophene (2) $>$ thiophene $>$ thieno[2,3-*b*]-thiophene (1); for free-radical substitution: thieno[3,4-*b*]-thiophene (3) $>$

²³⁸ A. Mangini, in "Molecular Structure and Spectroscopy," Int. Symp. Tokyo, 1962, p. 103. Butterworth, London, 1963.

²³⁹ G. R. Howe, *J. Chem. Soc. B*, 984 (1971).

²⁴⁰ E. Helgstrand, *Acta Chem. Scand.* **24**, 3587 (1970).

²⁴¹ E. Helgstrand, *Acta Chem. Scand.* **26**, 2024 (1972).

²⁴² W. Jakubetz and P. Schuster, *Angew. Chem.* **83**, 499 (1971).

²⁴³ J. T. Cleghorn, *J. Chem. Soc. Perkin Trans. II*, 479 (1972).

²⁴⁴ J. A. Pople and G. A. Segal, *J. Chem. Phys.* **44**, 3289 (1966).

²⁴⁵ D. P. Santry and G. A. Segal, *J. Chem. Phys.* **47**, 158 (1967).

thiophene > thieno[3,2-*b*]thiophene (2) > thieno[2,3-*b*]thiophene (1).

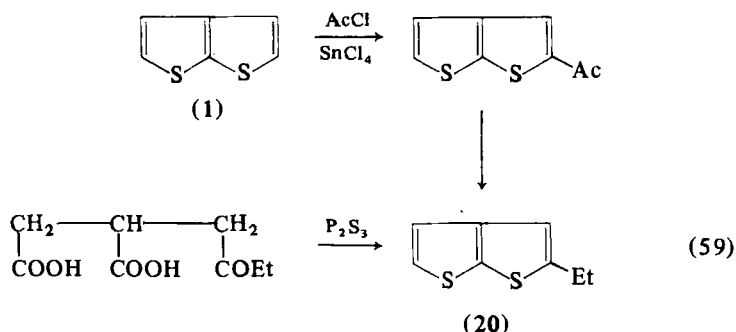
This order of reactivity was observed for acid dedeuteration,²¹⁹ but for acetylation, formylation, and chlorination it was slightly different: thieno[3,2-*b*]thiophene (2) > thieno[2,3-*b*]thiophene (1) > thiophene¹⁷⁹; thieno[3,4-*b*]thiophene (3) was not studied. A substantially greater discrepancy between theoretical and experimental data was observed for nucleophilic substitution; from the data on base dedeuteration²²⁸ and competitive metalation reactions,¹⁷¹ the order of decreasing reactivity was as follows: thieno[2,3-*b*]thiophene (1) > thieno[3,2-*b*]thiophene (2) > thiophene. To a certain extent this may be explained by differences in the mechanism of metalation and deuterium exchange with a base. A discrepancy between calculation and experiment was also found for free-radical substitution.⁶⁹

B. CHEMICAL CONVERSIONS OF THE ISOMERIC THIENOTHIOPHENES

In spite of the fact that thienothiophenes, particularly 1 and 2, have been known for a long time, their chemistry has received little attention, mainly owing to the absence of convenient synthetic methods. As can be seen in Section II, the situation is now changing for the better, and a detailed investigation is now feasible.

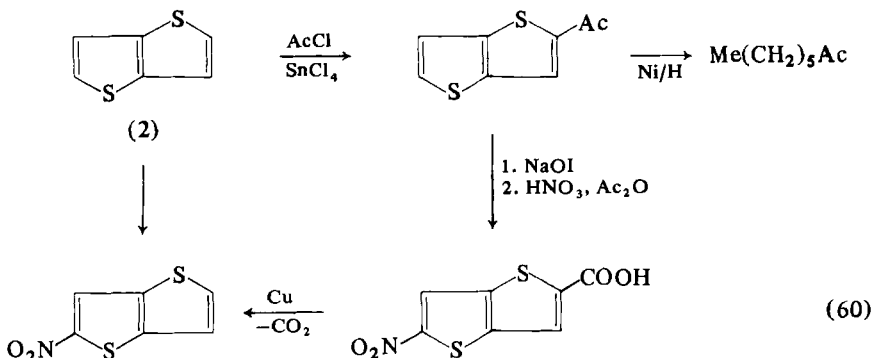
1. Acetylation

Alkyl aryl ketones are convenient intermediates for preparing other substituted aromatic and heteroaromatic compounds. Challenger and co-workers^{18-21,26} acetylated thieno[2,3-*b*]thiophene (1) with acetyl chloride and stannic chloride [Eq. (59)]. The 2-acetylthieno[2,3-*b*]thiophene obtained by this method was reduced to the 2-ethyl derivative (20) identical with the product of an independent synthesis.^{25,26}

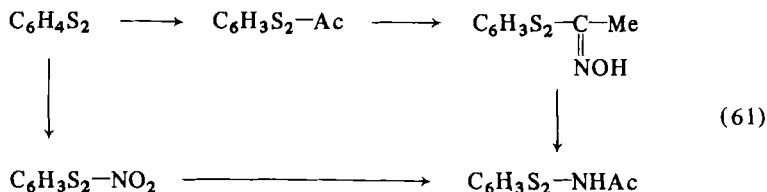


It was also shown, by Challenger and Gibson,²¹⁸ that the carboxylic acids formed on oxidation of 2-acetylthieno[2,3-*b*]thiophene and on metalation of thienothiophene 1 followed by carbonation, were identical.

Similarly, acetylation of thieno[3,2-*b*]thiophene (2) afforded 2-acetylthieno[3,2-*b*]thiophene, which was converted into methyl *n*-hexyl ketone by desulfurization with Raney nickel.^{25,28} Oxidation of 2-acetylthieno[3,2-*b*]thiophene followed by nitration gave 5-nitrothieno[3,2-*b*]thiophene-2-carboxylic acid. Decarboxylation of the latter furnished 2-nitrothieno[3,2-*b*]thiophene identical with the compound obtained by direct nitration of thienothiophene 2 [Eq. (60)].



The structures of the acetylation products of 1 and 2 were also proved by the following conversions.^{25,28} The oximes derived from the acetyl thienothiophenes gave the corresponding acylamino compounds on Beckman rearrangement. The latter were identical with the derivatives obtained by reduction (H_2/Ni) in acetic anhydride of the 2-nitro-substituted thienothiophenes 1 and 2 [Eq. (61)].

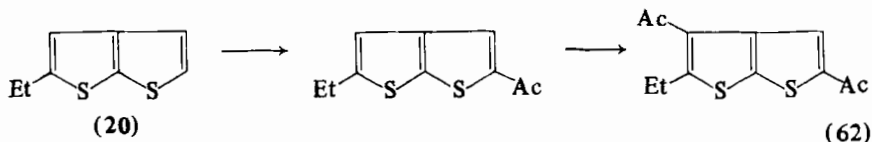


Propionylation ($EtCOCl/SnCl_4/CS_2$) of thienothiophene 2 readily gives (in 88% yield) 2-propionylthieno[3,2-*b*]thiophene.²¹⁸ With acetic anhydride and traces of iodine, 2 yields 2-acetylthieno[3,2-*b*]thiophene (50%).²⁰ The latter was also prepared by acetyl chloride treatment of the monomercury compound produced by mercuration ($HgCl_2$) of thienothiophene 2.²¹⁸

In 2-alkyl-substituted thienothiophenes 1 and 2 the free α -position is attacked.^{44,57,67,219} However, acetylation of 2-ethylthieno[2,3-*b*]-thiophene (20) produced, together with 2-acetyl-5-ethylthieno[2,3-*b*]-thiophene, small quantities of some other compound which was ascribed²¹⁹ the structure of 3-acetyl-2-ethylthieno[2,3-*b*]thiophene by analogy with the acetylation products of 2-ethylthiophene.²⁴⁶ Acetylation of 2,5-dialkylthienothiophenes 1 and 2, like 2,5-dialkylthiophenes,²⁴⁷ proceeds easily in the presence of stannic chloride. For example 2,5-diethylthieno[2,3-*b*]thiophene (with $\text{AcCl}/\text{SnCl}_4/\text{C}_6\text{H}_6$) forms 3-acetyl-2,5-diethylthieno[2,3-*b*]thiophene in 80% yield.⁶⁷

Acetylation of 3-ethylthieno[2,3-*b*]thiophene (21) gives 2-acetyl-3-ethylthieno[2,3-*b*]thiophene,²⁶ and acetylation of 3-methylthieno[3,2-*b*]thiophene (27) proceeds similarly (92% yield), while 2-ethyl-6-methylthieno[3,2-*b*]thiophene is converted into 2-acetyl-5-ethyl-3-methylthieno[3,2-*b*]thiophene (73%).⁴³

Diacylation is possible: acetyl chloride with 2-acetyl-5-ethylthieno[2,3-*b*]thiophene and excess of aluminum chloride (2.5 moles) formed 40% of 3,5-diacetyl-2-ethylthieno[2,3-*b*]thiophene⁶⁷ [Eq. (62)]. The yield was raised to 77% by using a large excess of acetyl chloride (5.5 moles per mole of thienothiophene).



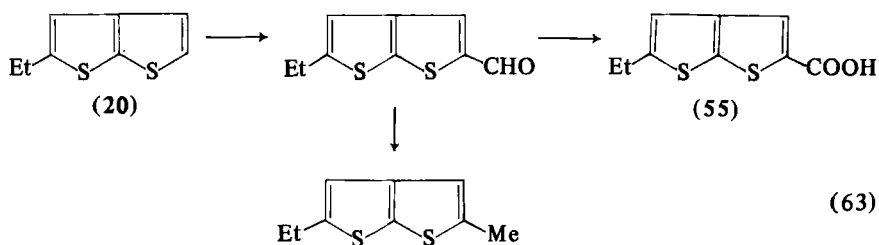
The formation of β -isomers during acylation of the unsubstituted thienothiophenes 1 and 2 was reported first in 1972 by Bugge,¹⁷⁹ who showed by gas-liquid chromatography and mass spectrometry that thienothiophenes 1 and 2 with acetic anhydride and SnCl_4 in dichloroethane at 25° affords the 2-acetyl derivatives (80% yields), containing up to 1% of 3-acetylthieno[2,3-*b*]thiophene and 0.8% of 3-acetylthieno[3,2-*b*]thiophene.

2. Formylation

Gol'dfarb and Litvinov first formylated a thienothiophene. In Vilsmeier formylation of 2-ethylthieno[2,3-*b*]thiophene (20) the formyl group enters the vacant α -position, producing 5-ethyl-2-formylthieno[2,3-*b*]thiophene (76%).⁴⁴ Oxidation of the latter with silver oxide gives 5-ethylthieno[2,3-*b*]thiophene-2-carboxylic acid (55) identical with that formed by cyclizing the ester of (5-ethyl-3-formyl-2-thienylthio)acetic

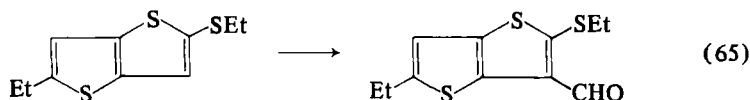
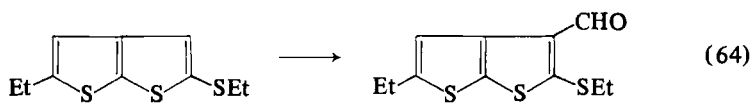
²⁴⁶ S. Gronowitz and J. E. Scramstad, *Ark. Kemi* 28, 115 (1967).

²⁴⁷ H. D. Hartough, "Thiophene and Its Derivatives." Wiley (Interscience), New York, 1952.

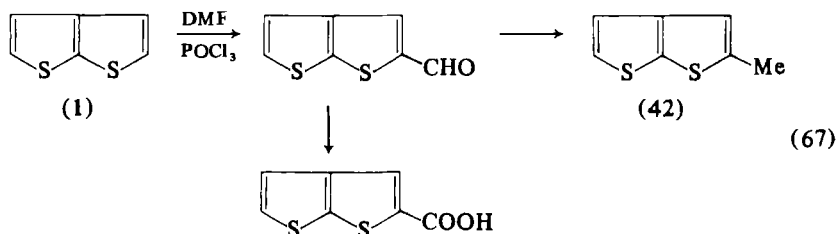
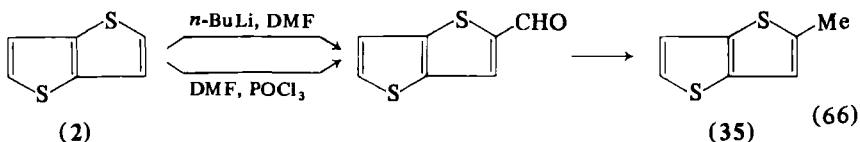


acid (54).⁵³ Wolff-Kishner reduction of 5-ethyl-2-formylthieno[2,3-*b*]-thiophenes leads to 2-ethyl-5-methylthieno[2,3-*b*]thiophene in 70% yield⁴⁴ [Eq. (63)].

When α -positions in thienothiophenes 1 and 2 are both blocked, the formyl group enters a β -position. Thus, formylation of 5-ethyl-2-ethylthiothieno[2,3-*b*]thiophene and 5-ethyl-2-ethylthiothieno[3,2-*b*]thiophene afforded high yields of the 3-formyl derivatives²²⁰ [Eqs. (64) and (65)]. 2-Ethylthiobenzo[*b*]thiophene reacts analogously.

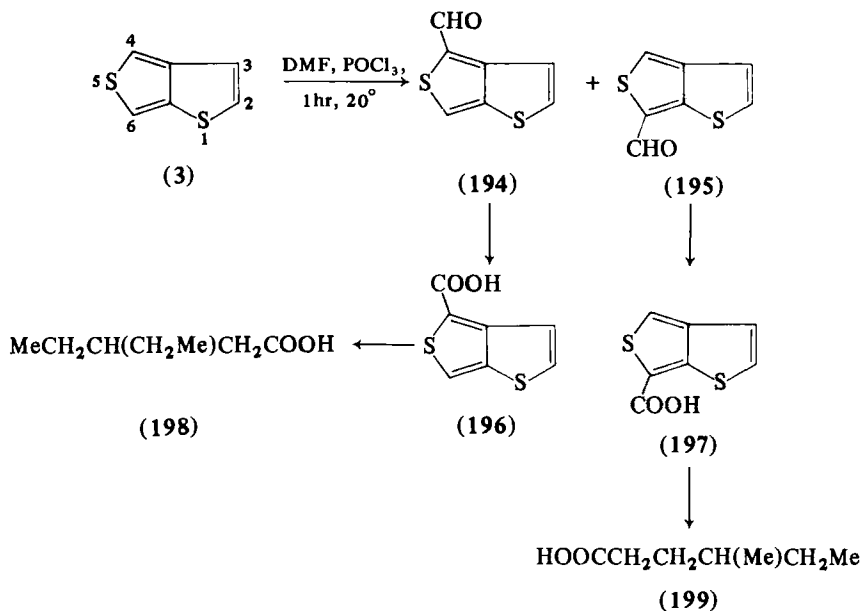


Unsubstituted thienothiophenes 1 and 2 are smoothly formylated in the 2-positions by DMF-phosphorus oxychloride in dichloroethane.^{68,179} The site of substitution in thienothiophene 2 was confirmed by preparing the corresponding formyl derivative from 2-lithiothieno[3,2-*b*]thiophene and DMF, and in the case of 1, by oxidizing the formyl derivative to thieno[2,3-*b*]thiophene-2-carboxylic acid, as well as the NMR spectra⁶⁸ [Eqs. (66) and (67)].



Mass spectrometry and gas-liquid chromatography showed 3-formylthieno[2,3-*b*]thiophene (0.2%) in the crude product from 1.¹⁷⁹ While diformyl derivatives were not observed from 2 with two equivalents of DMF, small quantities of the diformyl derivatives were detected by mass spectrometry in the case of thienothiophene 1.⁶⁸ Italian researchers obtained 2,5-diformylthieno[3,2-*b*]thiophene by the action of *n*-butyllithium and dimethyl formamide on 2,5-dibromothieno[3,2-*b*]thiophene.¹⁸⁹

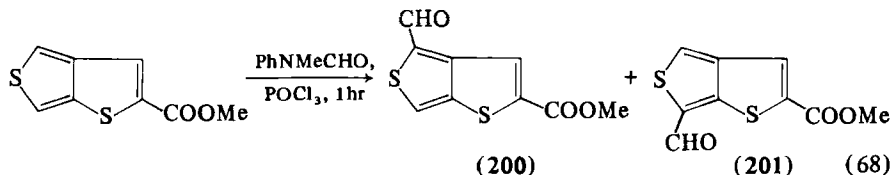
Wynberg and Feijen¹⁶⁷ studied thieno[3,4-*b*]thiophene (3) formylation and found that both positions 4 and 6 are attacked. This is in accordance with theoretical predictions.^{154,156} The reaction produces a mixture (7:3) of 4-formyl- (194) and 6-formylthieno[3,4-*b*]thiophene (195) in 56% total yield after separation and purification. The formyl derivatives obtained were oxidized to the corresponding carboxylic acids 196 and 197, which were converted into 3-ethylpentanoic 198 and 4-methylhexanoic (199) acids by desulfurization with Raney nickel [Scheme 15].



SCHEME 15

More vigorous conditions were required for the formylation of thienothiophene 3 with an electron acceptor group in the molecule. Thus, refluxing methyl thieno[3,4-*b*]thiophene-2-carboxylate, *N*-methylformanilide and phosphorus oxychloride for 1 hour gave a mixture (1:1)

of methyl 4-formylthieno[3,4-*b*]thiophene-2-carboxylate (**200**) and methyl 6-formylthieno[3,4-*b*]thiophene-2-carboxylate (**201**) in 40% total yield [Eq. (68)].



By DMF and phosphorus oxychloride, dithieno[3,2-*b*:2',3'-*d*]thiophene (**6**) was converted into the 2-formyl derivative in 93% yield.¹²¹ The production of 2,6-diformyldithieno[3,2-*b*:2',3'-*d*]thiophene has been reported, without experimental data.¹⁹⁰

3. Halogenation

Biedermann and Jacobson,² who first prepared thieno[2,3-*b*]thiophene (**1**) in 1886, characterized it as a 2,3,4,5-tetrabromo derivative with m.p. 172°. Later Capelle⁵ reported the isolation of a "dibromo derivative" of thienothiophene **1** with m.p. 122.5°, which was shown by Challenger and Harrison¹⁸ to be 2,3,5-tribromothieno[2,3-*b*]thiophene (m.p. 123°–124°). Capelle⁵ also obtained a tetrabromide, m.p. 223°, by bromination of the product of reaction of acetylene with sulfur. The tetrabromide seems to be identical with that prepared from the product of reaction of methane, acetylene, and hydrogen sulfide, m.p. 229°–230°, and is evidently 2,3,5,6-tetrabromothieno[3,2-*b*]thiophene.¹⁸

Attempts to synthesize a monobromo derivative by treating thienothiophene **2** with one equivalent of bromine in glacial acetic acid resulted in a dibromo derivative and polymer.²² Similar polymers were obtained from thienothiophenes **1** and **2** with hydrogen bromide in acetic acid.²²

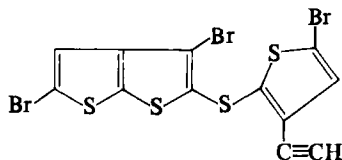
Bugge¹⁷² brominated thienothiophenes **1** and **2** with *N*-bromosuccinimide in glacial acetic acid to 2-bromothieno[2,3-*b*]thiophene (66%) and 2-bromothieno[3,2-*b*]thiophene (55%). The structure of 2-bromothieno[2,3-*b*]thiophene was confirmed by the replacement of bromine by lithium at –70° followed by carbonation to thieno[2,3-*b*]thiophene-2-carboxylic acid; 2-bromothieno[3,2-*b*]thiophene was independently prepared by the treatment of 2-lithiothieno[3,2-*b*]thiophene with one equivalent of bromine at –70°. The 2-bromo derivatives of thienothiophenes **1** and **2** decompose within several hours at 20°, but remain unchanged for weeks at –15°.

IR spectroscopy has shown that thienothiophenes 1 and 2 are brominated with *N*-bromosuccinimide to furnish dibromo along with monobromo derivatives.¹⁷² An unpurified bromination product of thienothiophene 1 contained 8% of the initial thienothiophene 1, 83% of 2-bromothieno[2,3-*b*]thiophene, and 9% of 2,5-dibromothieno[2,3-*b*]thiophene; 15% of the initial thienothiophene 2, 70% of 2-bromothieno[3,2-*b*]thiophene and 15% of 2,5-dibromothieno[3,2-*b*]thiophene were detected on bromination of thienothiophene 2.¹⁷²

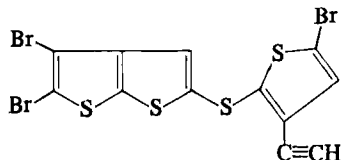
Bromination by two equivalents of *N*-bromosuccinimide in glacial acetic acid gave good yields (65% and 88%) of 2,5-dibromo derivatives of thienothiophenes 1 and 2, and 2,3,5-tribromo derivatives were obtained using three equivalents of bromine in carbon disulfide (75% and 81% yields).¹⁷²

Treatment of 2,3,5-tribromothieno[3,2-*b*]thiophene with *n*-butyllithium followed by hydrolysis produced 74% yield of 2,6-dibromothieno[3,2-*b*]thiophene, and treatment with zinc dust in glacial acetic acid formed 3-bromothieno[3,2-*b*]thiophene, containing unsubstituted thienothiophene 2 and the 2,6-dibromo compound as impurities. Pure 3-bromothieno[3,2-*b*]thiophene was isolated using preparative gas-liquid chromatography.¹⁷² 2,3,5-Tribromothieno[2,3-*b*]thiophene similarly afforded 3-bromothieno[2,3-*b*]thiophene.

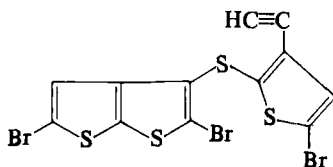
Attempts to synthesize 2,4-dibromothieno[2,3-*b*]thiophene by reaction of 2,3,5-tribromothieno[2,3-*b*]thiophene with *n*-butyllithium at -70° gave a mixture of the initial tribromide and a compound of composition $C_{12}H_3Br_3S_4$, to which structure 202 was ascribed on the basis of IR, NMR, MS, although structures (203) and (204) were not excluded.



(202)



(203)



(204)

5-Ethylthieno[2,3-*b*]thiophene-2-carboxylic acid with bromine in acetic acid gave the 4-bromo acid.⁴⁴

Iodination and chlorination have been considerably less studied. Data on iodination are limited to those of Challenger and co-workers, who showed that thienothiophenes **1**¹⁹ and **2**²⁰ with iodine and mercuric oxide give rather unstable 2-iodo derivatives, the structures of which were confirmed by their conversion into the corresponding 2-carboxylic acids.²⁰ The formation of 2,5-diiodothieno[3,2-*b*]thiophene by iodination of **2** was also observed.²²

Wynberg and co-workers²⁴⁸ obtained 2,5-dichlorothieno[2,3-*b*]thiophene from thienothiophene **1** with sulfonyl chloride in CCl₄ at -5°.

With one equivalent of *N*-chlorosuccinimide (NCS) in acetic acid at 25°, thienothiophene **1** gives the initial thienothiophene **1** (11%), 2-chloro- (78%) and 2,5-dichlorothieno[2,3-*b*]thiophene (10%), while a 70% yield of 2,5-dichlorothieno[2,3-*b*]thiophene is produced with two equivalents of NCS.¹⁷⁹ Similar results were obtained from thienothiophene **2** with one and two equivalents of NCS. About 0.4% 3-chlorothieno[2,3-*b*]thiophene was detected by gas-liquid chromatography among the chlorination products of **1**. The same amount of β -isomer is found in thiophene chlorination products. In the case of thienothiophene **2**, the corresponding β -isomer was not observed in the reaction products. To identify 3-chloro-substituted thiophene and thienothiophenes **1** and **2** in reaction mixtures, these compounds were prepared independently from the corresponding 3-bromo derivatives by lithiation followed by chlorination at -70°.

Since bromination and chlorination result in a greater variety of di-substituted products of thieno[2,3-*b*]thiophene **1** than of thieno[3,2-*b*]thiophene **2**, the conclusion has been drawn¹⁷⁹ that a halogen in position 2 in thienothiophene **1** deactivates position 5 to a lesser extent than in thienothiophene **2** and that the halogen deactivating effect in **1** is similar to that in thiophene.

Synthetic methods involving halogenation with ring formation have been mentioned earlier (Section II, B), as has the preparation of octafluorooctahydrodithieno[2,3-*b*:2',3'-*d'*]thiophene (**190**) from sulfur, tetrafluoroethylene, and thiophene.^{125,126}

4. Nitration

Nitration of thienothiophenes **1** and **2** occurs at position 2. Challenger *et al.*^{18,20-22,26} showed that concentrated nitric acid in acetic anhydride furnished 2-nitrothieno[2,3-*b*]thiophene (**205**) and 2-nitrothieno[3,2-*b*]thiophene, respectively.¹⁸ The latter was converted into the 2,5-dinitro compound with more nitric acid.²²

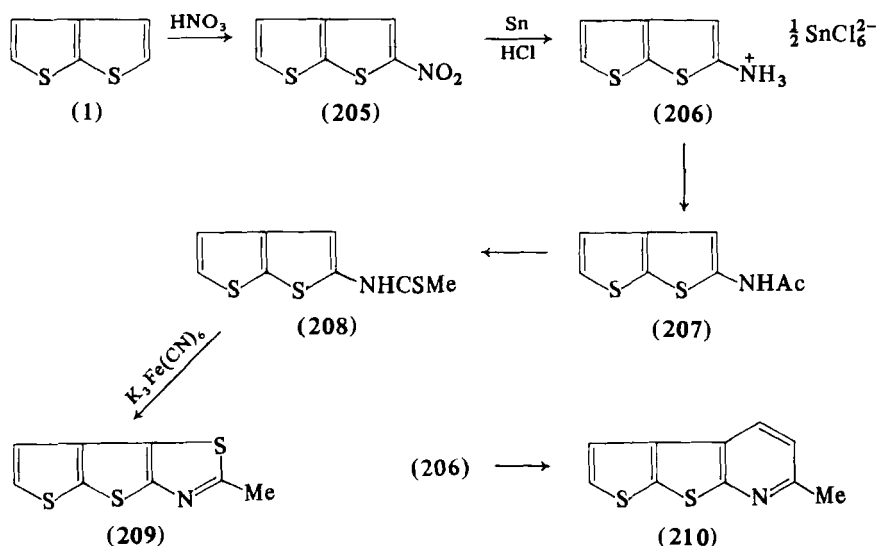
²⁴⁸ S. H. Wilen, G. J. Douma, and H. Wynberg, *Rec. Trav. Chim. Pays-Bas* **89**, 980 (1970).

Nitration of 3-ethylthieno[2,3-*b*]thiophene (21) afforded the 2-nitro derivative.²⁶ Even when one α -position is occupied by a deactivating electron acceptor group (COOH, Ac), the nitro group enters the other α -position. Thus, nitration (HNO_3/AcOH) of 2-acetylthieno[2,3-*b*]thiophene gives the 5-nitro compound identical with the product of acetylation ($\text{AcCl}/\text{AlCl}_3/\text{CS}_2$) of 2-nitrothieno[2,3-*b*]thiophene.²⁰ Nitration ($\text{HNO}_3/\text{Ac}_2\text{O}$) of thieno[2,3-*b*]thiophene-2-carboxylic acid proceeds similarly, yielding 5-nitro acid which can be decarboxylated to 2-nitrothieno[2,3-*b*]thiophene.²⁰ 5-Nitrothieno[2,3-*b*]thiophene-2-carboxylic acid was also prepared in low yield by oxidation of the 2-acetyl-5-nitro derivative.²⁰

Beckmann rearrangement ($\text{SOCl}_2/\text{Me}_2\text{CO}$) of the oximes of 2-acetylthieno[2,3-*b*] and [3,2-*b*]thiophene leads to the formation of 2-acetamidothienothiophenes identical with those obtained by reductive acetylation ($\text{H}_2/\text{Ni}/\text{Ac}_2\text{O}$) of the 2-nitro compound.²⁰

Nitration of thienothiophenes 1 and 2 with $\text{Cu}(\text{NO}_3)_2 \cdot 3\text{H}_2\text{O}$ in acetic anhydride afforded the 2-nitro compounds in 30% and 56% yields, respectively. Gas-liquid chromatography showed the presence of 3-nitrothieno[3,2-*b*]thiophene (up to 0.9%) and 3-nitrothieno[2,3-*b*]thiophene (3–5%) in the crude reaction products.¹⁷⁹

Reduction (Sn/HCl) of 2-nitrothieno[2,3-*b*]thiophene (205) gives a salt (206) which can be converted into 2-acetamidothieno[2,3-*b*]thiophene (207). From 207 and P_2S_5 , the 2-thioacetamido analog (208) was obtained; oxidation of this with ferricyanide yielded 13% of 2-



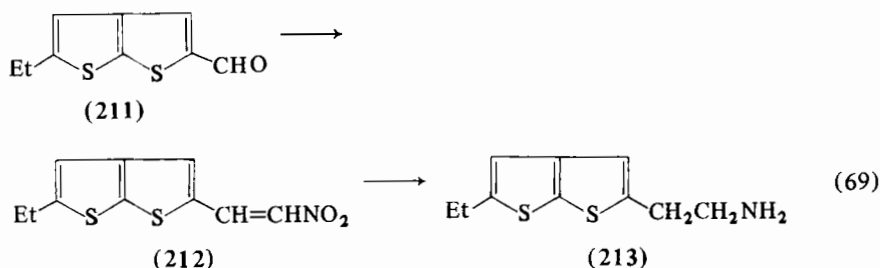
SCHEME 16

methylthieno[2,3-*b*]thieno[2,3-*d*]thiazole (209).^{249,250} Condensation of the stannichloride 206 with acetoacetaldehyde diethylacetal afforded 23% of 2-methylthieno[2,3-*b*]thieno[2,3-*b*]pyridine (210).^{250,251} (Scheme 16).

In a similar way, 2-methylthieno[3,2-*b*]thieno[2,3-*b*]pyridine was prepared from 2-nitrothieno[3,2-*b*]thiophene.^{251,252}

Condensation (FeCl_3 , ZnCl_2 , HCl) of these amine salts with methyl vinyl ketone produced 4-methylthieno[2,3-*b*]thieno[2,3-*b*]pyridine and 4-methylthieno[3,2-*b*]thieno[2,3-*b*]pyridine, respectively^{253,254}, while acetylacetone (ZnCl_2) afforded the 2,4-dimethyl derivatives.^{255,256}

5-Ethyl-2-formylthieno[2,3-*b*]thiophene (211) and nitromethane by the Knoevenagel method²⁵⁷ gave 2- β -nitrovinyl-5-ethylthieno[2,3-*b*]thiophene (212) (73%); reduction (LAH) of 212 led to the 2- β -aminoethyl analog (213)⁴⁴ [Eq. (69)].



5. Oxidation

Oxidation of acetyl- and acetylnitro-substituted thienothiophenes 1 and 2 with ferricyanide or hypoiodite to the corresponding acids was used primarily to confirm the site of electrophilic substitution at position 2 in the thienothiophenes.^{18-21,218} Permanganate degrades the thieno[3,2-*b*]thiophene (2) ring system, while potassium hypobromite produced bromo derivatives of thieno[2,3-*b*]thiophene-2-carboxylic acid.^{18,218}

²⁴⁹ V. G. Zhiryakov and P. I. Abramenko, *Khim. Geterotsikl. Soedin.*, 619 (1965).

²⁵⁰ V. G. Zhiryakov and P. I. Abramenko, *Avtorsk. Svid. SSSR*, No. 166702; *Byull. Izobret. Tovarnykh Znakov* 23, 25 (1964).

²⁵¹ V. G. Zhiryakov and P. I. Abramenko, *Khim. Geterotsikl. Soedin.*, 334 (1965).

²⁵² P. I. Abramenko and V. G. Zhiryakov, *Avtorsk. Svid. SSSR* No. 165731; *Byull. Izobret. Tovarnykh Znakov* 20, 16 (1965).

²⁵³ V. G. Zhiryakov and P. I. Abramenko, *Avtorsk. Svid. SSSR*, No. 166699; *Byull. Izobret. Tovarnykh Znakov* 23, 24 (1964).

²⁵⁴ P. I. Abramenko and V. G. Zhiryakov, *Khim. Geterotsikl. Soedin.*, 139 (1966).

²⁵⁵ P. I. Abramenko, *Khim. Geterotsikl. Soedin.*, 368 (1967).

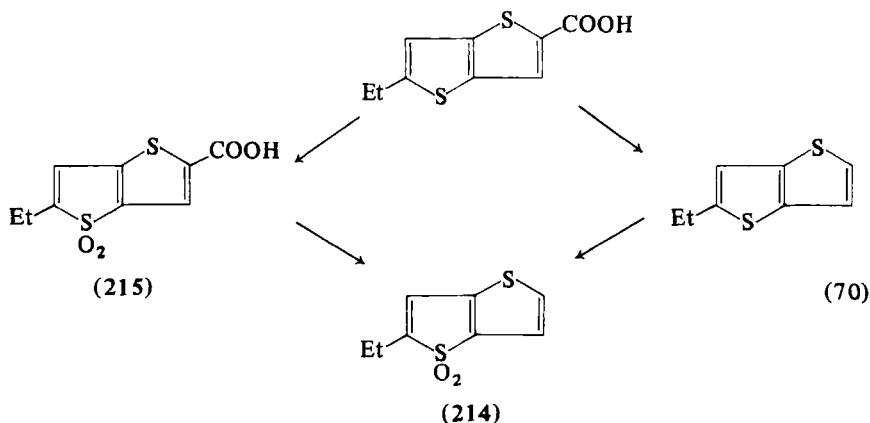
²⁵⁶ P. I. Abramenko, *Khim. Geterotsikl. Soedin.*, 468 (1971).

²⁵⁷ W. Knoevenagel, *Ber.* 37, 4507 (1904).

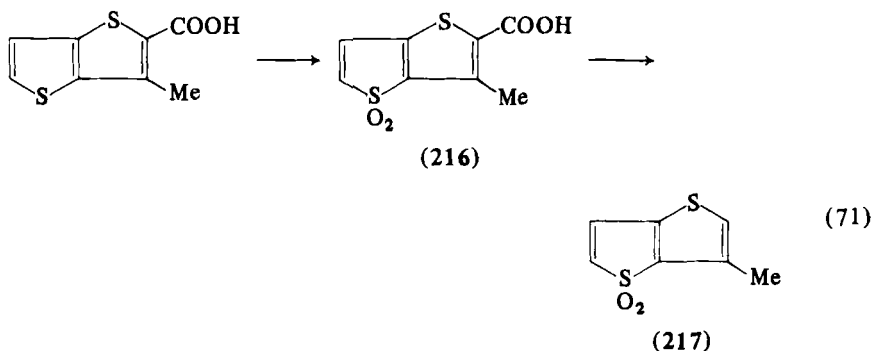
Oxidation of the acetyl group in 2-acetyl-3,5-dialkyl derivatives of **1** and **2** with iodine in pyridine,^{39,44} and of the formyl group in 5-ethyl-2-formyl-⁴⁴ and 2-formylthieno[2,3-*b*]thiophene,⁶⁸ and 4-formyl- and 6-formylthieno[3,4-*b*]thiophene (**194** and **195**)¹⁶⁷ with silver oxide, was performed to verify the structures of the acetylation and formylation products.

In 1948 Maxted and Walker²¹¹ studied the detoxification of catalyst poisons in the hydrogenation of aromatic hydrocarbons and found that the isomeric thienothiophenes **1** and **2** could be converted into the sulfones of fully hydrogenated thienothiophenes **1** and **2**, which do not poison the catalysts. This conversion is performed by brief preliminary hydrogenation and subsequent oxidation by hydrogen peroxide or permolybdic acid. However, no data on the isolation or the properties of these disulfones are available. It has been reported²¹¹ that direct oxidation of thienothiophenes **1** and **2** does not produce sulfones.

Incorporating an electron-donor alkyl group into position 2 of **2** was shown by the present authors⁵⁷ to facilitate S-oxidation; thus, 2-ethylthieno[3,2-*b*]thiophene-1,1-dioxide (**214**) was prepared at 40°–45° from 2-ethylthieno[3,2-*b*]thiophene, hydrogen peroxide and acetic acid. The thieno[3,2-*b*]thiophene system undergoes oxidation even if the second α -position is carboxy-substituted; oxidation of 5-ethylthieno[3,2-*b*]thiophene-2-carboxylic acid furnished the 4,4-dioxide (**215**) subsequently decarboxylated to sulfone (**214**) [Eq. (70)]. The [2,3-*b*] isomers, **20** and **55**, with the sulfur atoms bound to the same carbon atom, do not form sulfones under similar conditions.



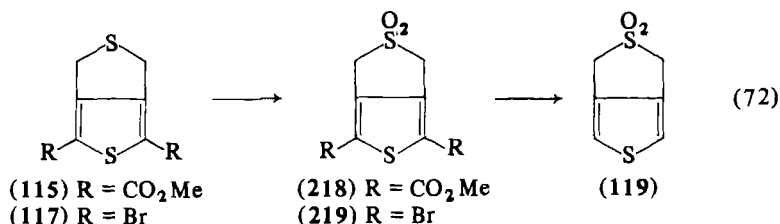
S-oxidation of 3-methylthieno[3,2-*b*]thiophene-2-carboxylic acid⁶³ yields 63% of the 4,4-dioxide (**216**), converted into 3-methylthieno[3,2-*b*]thiophene-4,4-dioxide (**217**) by decarboxylation [Eq. (71)]. The structures of the sulfones **214**–**217** were confirmed by IR, UV, and NMR.^{57,63}



The 1,1-dioxide (22%) is formed by oxidation of 2,5-dimethylthieno[3,2-*b*]thiophene with *m*-chloroperbenzoic acid in methylene chloride at -20° .¹⁶²

Wynberg *et al.*⁹¹ oxidized dimethyl 1*H*,3*H*-thieno[3,4-*c*]thiophene-4,6-dicarboxylate (115) with H_2O_2 -HOAc to the dioxide 218 (55%) [Eq. (72)].

Similarly 4,6-dibromo-1*H*,3*H*-thieno[3,4-*c*]thiophene (117) affords 90% of the 2,2-dioxide (219); the last can be debrominated to 1*H*,3*H*-thieno[3,4-*c*]thiophene-2,2-dioxide (119) with zinc in acetic acid⁹³ [Eq. (72)].



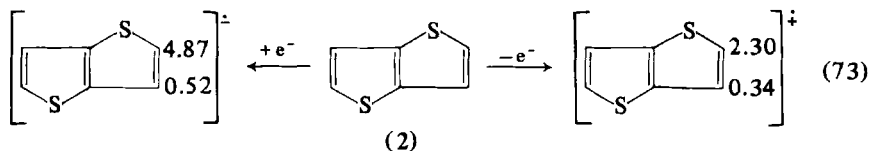
Analogous oxidation of methyl 4,6-dihydrothieno[3,4-*b*]thiophene-2-carboxylate (134) leads to the 5,5-dioxide (135) (70%); hydrolysis and subsequent oxidation with sodium metaperiodate at 0° (cf. Leonard and Johnson²⁵⁸) results in 2-carboxy-4,6-dihydrothieno[3,4-*b*]thiophene-5-oxide (91) (74%).²³

4,6-Dimethyl-1*H*,3*H*-thieno[3,4-*c*]thiophene (142) with sodium periodate in methanol⁹⁹ yields the 2-oxide (143) (91%), and 1,3,4,6-tetraphenyl-1*H*,3*H*-thieno[3,4-*c*]thiophene (147) behaves analogously¹⁰⁰ to form 148 (96%).

Vigorous oxidation (CrO_3/HOAc) of 1,3,4,6-tetraphenylthieno[3,4-*c*]thiophene (149) opens a ring, to yield 3,4-dibenzoyl-2,5-diphenylthiophene (60%).¹⁰³

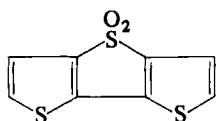
²⁵⁸ N. J. Leonard and C. R. Johnson, *J. Org. Chem.* 27, 282 (1962).

As stated in the previous section, reduction of thieno[3,2-*b*]thiophene (2) with Na-K alloy at -100° results in the formation of a radical-anion.^{187,188} With AlCl_3 in nitromethane at -20° , or SbCl_5 in methylene chloride at -60° , a radical-cation was obtained.²³⁷ The experimental hyperfine splitting constants (HFSC) data are shown in Eq. (73).

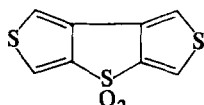


This, after 1,3,6,8-tetraazapyrene,²⁵⁹ was only the second example of obtaining both a negative and a positive radical from the same heterocyclic compound. Attempts to generate radical-ions from other condensed thiophenes succeeded only with dithieno[2,3-*b*:2',3'-*d*]thiophene (10) radical-cation [HFSC 0.42 (2H), 2.36 (1H), and 2.98 (1H) Gauss].

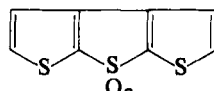
Condensation of three thiophene rings, as in dithienothiophenes (5–10), results in a greater reactivity toward oxidizing agents such as peracids, the sulfur atom of the central ring being attacked.^{121,123,124} Dithieno[3,2-*b*:2',3'-*d*]thiophene (6) and dithieno[3,4-*b*:3',4'-*d*]thiophene (7) produce good yields of sulfones 220 and 221 with H_2O_2 -HOAc,^{121,123} but, dithieno[2,3-*b*:3',2'-*d*]thiophene (5) and dithieno[2,3-*b*:3',4'-*d*]thiophene (8) under these conditions form only small amounts



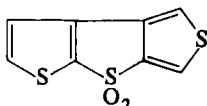
(220)



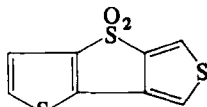
(221)



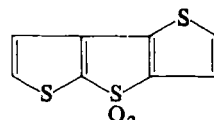
(222)



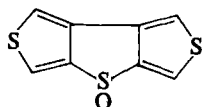
(223)



(224)



(225)



(226)

²⁵⁹ F. Gerson, *Helv. Chim. Acta* 47, 1484 (1964).

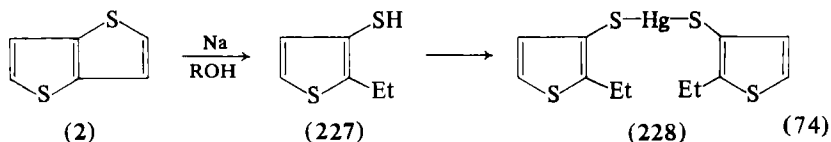
of impure sulfones 222 and 223.¹²³ However, 5 and 8 and also dithieno[3,2-*b*:3',4'-*d*]thiophene (9) and dithieno[2,3-*b*:2',3'-*d*]thiophene (10), are oxidized to the respective sulfones (222–225) in good yields with *m*-chloroperbenzoic acid in methylene chloride.^{123,124} Although the formation of intermediate sulfoxides was established by thin-layer chromatography, the pure sulfoxide (226) was isolated and characterized¹²³ only for dithienothiophene 7.

The presence and position of the sulfone grouping was confirmed by IR and NMR spectra,^{123,124} and for sulfone (220) by an independent synthesis.¹²¹

6. Reduction

As already mentioned (Section III,D), reduction with sodium potassium alloy at -100° of thieno[3,2-*b*]thiophene (2) generates a short-lived radical-anion on the alloy surface.^{187,188,237}

Sodium in alcohol opens one thiophene ring of thienothiophene (2) to give 2-ethyl-3-mercaptothiophene (227), which was characterized as its mercury derivative (228)¹⁸ [Eq. (74)].



Similar reduction of benzo[*b*]thiophene furnishes the 2,3-dihydro derivative and *o*-ethylthiophenol.²⁶⁰

Maxted and Walker²¹¹ showed that the isomeric thienothiophenes 1 and 2 are hydrogenated over platinum at atmospheric pressure and 27° without C–S bonds being broken.

Catalytic reduction of 1,3,4,6-tetraphenylthieno[3,4-*c*]thiophene (149) in the presence of a large amount of Pd/C gives a good yield of 1,3,4,6-tetraphenyl-1*H*,3*H*-thieno[3,4-*c*]thiophene (147).¹⁰³

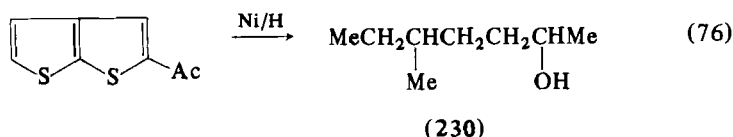
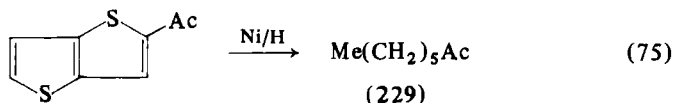
Reduction by LiAlH_4 of 2,3-dihydrothieno[3,2-*b*]thiophen-3-one (22) and its 2-methyl- and 2-ethyl-derivatives afforded the appropriate thienothiophene 2.^{21,25,28,29} Similarly, Gronowitz and co-workers⁴⁸ used borohydride reduction of ketones 33 and 34 to prepare 2-methylthieno[3,2-*b*]thiophene (35). Attempts to reduce 2,3-dihydrothieno[3,2-*b*]thiophen-3-one (22)²⁸ and 2,3-dihydro-4,6-dimethylthieno[3,4-*b*]thiophen-3-one (87)⁷⁵ with zinc powder in acetic acid were unsuccessful.

²⁶⁰ R. Fricke and G. Spilker, *Ber. B* 58, 24, 1589 (1926).

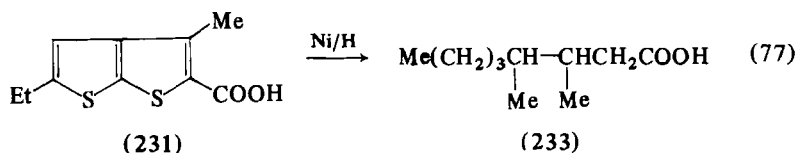
Alkyl-substituted thienothiophenes can be prepared by reducing acetyl or formyl derivatives (see refs. 18, 21, 25, 26, 28, 44, 57, 67, 68). Wolff-Kishner reduction is preferred to the Clemmensen method, since the latter requires hot concentrated hydrochloric acid, which may cause resinification.²⁶

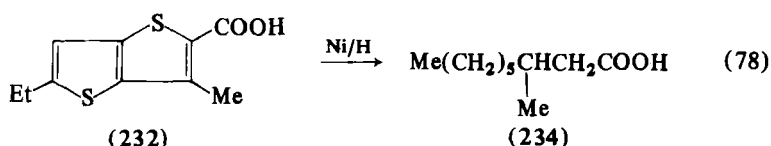
7. Reductive Desulfurization

Thienothiophenes, like thiophenes and benzo[*b*]thiophenes, easily undergo reductive desulfurization with Raney nickel. The method was first applied in this series by Challenger *et al.*^{21,25,28} to determine the structures of 2-acetylthieno[3,2-*b*]thiophene and 2-acetylthieno[2,3-*b*]thiophene; the former gave 2-octanone (229), and the latter 5-methylheptan-2-ol (230) [Eqs. (75) and (76)].

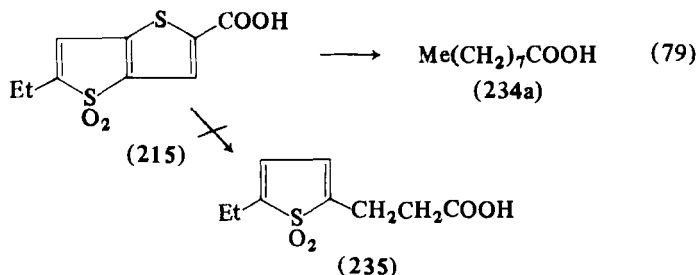


Reductive desulfurization was used by the present authors⁵⁷ to establish the structures of the products formed by AlCl_3 -catalyzed cyclization of 2-acetylthio-5-ethylthiophene. The mixture obtained of 5-ethyl-3-methylthieno[2,3-*b*]thiophene (26) and 5-ethyl-3-methylthieno[3,2-*b*]thiophene (27) was converted (AcCl/SnCl_4) into 2-acetyl-5-ethyl-3-methylthieno[2,3-*b*]thiophene and 2-acetyl-5-ethyl-3-methylthieno[3,2-*b*]thiophene. The individual ketones were isolated by fractional recrystallization,³⁹ and converted into the corresponding carboxylic acids (231 and 232). Desulfurization with Raney nickel furnished 3,4-dimethylcaprylic (233) and 3-methylpelargonic (234) acids [Eqs. (77), (78)].⁵⁷ Reductive desulfurization of 5-ethylthieno[2,3-*b*]thiophene-2-carboxylic and 5-ethylthieno[3,2-*b*]thiophene-2-carboxylic acids to 4-methylcaprylic (233) and pelargonic (234a) acids, was also studied.⁵⁷

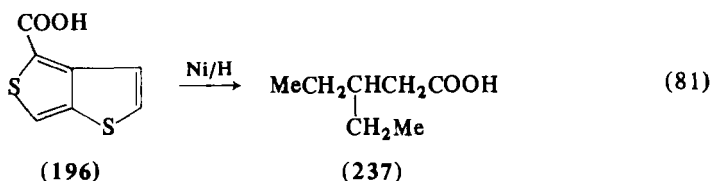
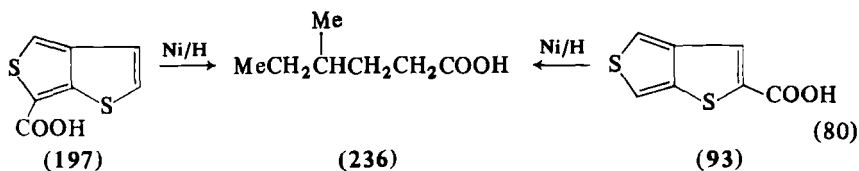




Desulfurization of the sulfone **215** afforded pelargonic acid (**234a**) rather than the expected sulfone (**235**)⁵⁷ [Eq. (79)].



Wynberg and Feijen¹⁶⁷ prepared δ -methylhexanoic acid (**236**) by desulfurization of thieno[3,4-*b*]thiophene-2-carboxylic (**93**) and 6-carboxylic (**197**) acids [Eq. (80)]. The analogous reaction with thieno[3,4-*b*]thiophene-4-carboxylic acid (**196**) produce 3-ethylpentanoic acid (**237**) [Eq. (81)].



8. Chloromethylation

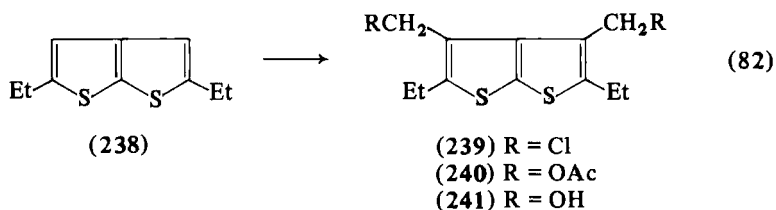
The preparation and reactivity of many chloromethyl thiophenes have been described.^{93,261-263} Paraformaldehyde and HCl at 50° produces

²⁶¹ Ya. L. Gol'dfarb and M. S. Kondakova, *Izv. Akad. Nauk SSSR, Otd. Khim. Nauk*, 495 (1956).

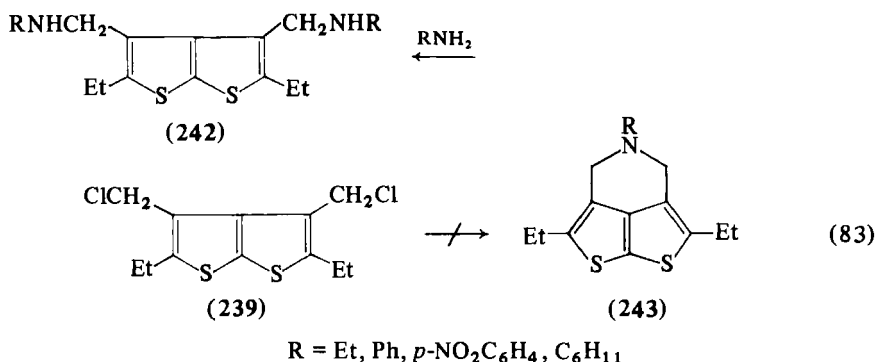
²⁶² Ya. L. Gol'dfarb and M. S. Kondakova, *Izv. Akad. Nauk, Otd. Khim. Nauk*, 501 (1961).

²⁶³ M. S. Kondakova and Ya. L. Gol'dfarb, *Izv. Akad. Nauk, Otd. Khim. Nauk*, 590 (1958).

good yields of 3,4-bis(chloromethyl) derivatives from 2,5-dialkyl thiophene. The extension of this method to 2,5-diethylthieno[2,3-*b*]-thiophene (**238**) afforded 3,4-bis(chloromethyl)-2,5-diethylthieno[2,3-*b*]-thiophene (**239**) (82%).²⁶⁴ Sodium acetate treatment of **239** gave bis-acetoxymethyl compound (**240**), which with sodium ethoxide led to 2,5-diethyl-3,4-bis(hydroxymethyl)thieno[2,3-*b*]thiophene (**241**) [Eq. (82)].



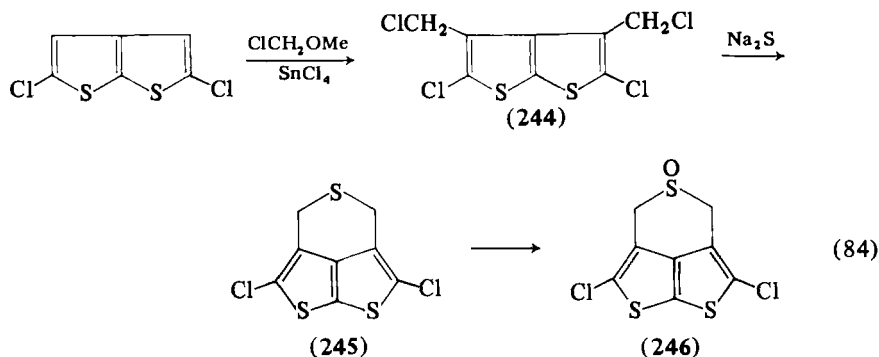
In a search for routes to periannulated systems containing a thienothiophene fragment, the reactions of **239** with primary amines (ethylamine, aniline, *p*-nitroaniline, and cyclohexylamine) were studied.²⁶⁴ The ratio of dichloromethyl thienothiophene to amine varied from 1:1 to 1:4, but only diamines **242** were found, and no periannulated compounds of type **243** [Eq. (83)].



On the basis of the formal similarity between 1,8-diaminonaphthalene and 3,4-diaminothiophene (1) the latter might be able to form a fused pyrimidine system on reaction with orthoformic ester or formamide.⁸⁵ However, heating dimethyl 3,4-diaminothiophene-2,5-dicarboxylate with acetic anhydride gave the corresponding *N,N'*-diacetyl derivative, while 3,4-diacyloxy derivatives resulted from analogous reaction of dimethyl 3,4-dihydroxythieno[2,3-*b*]thiophene-2,5-dicarboxylate with orthoformic ester and acetic anhydride.⁸⁵

²⁶⁴ Ya. L. Gol'dfarb, V. P. Litvinov, and S. A. Ozolin, *Khim. Geterotsikl. Soedin.*, 678 (1965).

The failure to prepare periannulated systems was ascribed to the substituents at positions 3 and 4 in thienothiophene 1 being much farther apart than those in the *peri* positions of naphthalene.^{85,264} Wynberg and co-workers²⁴⁸ therefore supposed that the substitution of sulfur for oxygen or nitrogen as the bridging heteroatom might have the desired effect. In this case cyclization is favored not only by the increase in C—S bond length in comparison with C—O or C—N, but also by the enhanced nucleophilic activity of the CH₂S group.^{93,265} Indeed, from 2,5-dichloro-3,4-bis(chloromethyl)thieno[2,3-*b*]thiophene (244), prepared as indicated, a 52% yield of 1,4-dichloro-5*H*,7*H*-2,3,6-trithiacyclopent-[*cd*]indene (245) was obtained by refluxing with sodium sulfide in methanol [Eq. (84)]. Compound 245 was oxidized to the sulfoxide (246).



9. Preparation of Organometallic Compounds

Challenger and co-workers^{18,19,21,22} first used mercuration (HgCl_2) to isolate and purify the thienothiophenes from the reaction of acetylene with sulfur. Thieno[3,2-*b*]thiophene gave a mixture of mercury derivatives with mercuric chloride both in the presence and in the absence of sodium acetate. The 2-monochloromercury derivative was isolated and converted to the corresponding acylthieno[3,2-*b*]thiophene with acetyl or propionyl chloride.^{21,218} The reaction of thienothiophene 2 with mercuric acetate affords the 2-acetoxymcury derivative.²⁰

Thienothiophenes 1 and 2 with ethylmagnesium bromide afford organometallic derivatives that can be carbonated to form the 2-carboxylic acids identical with those prepared by oxidation of the 2-acetyl derivatives.^{19-21,26,218} Thieno[3,2-*b*]thiophene-2,5-dicarboxylic acid was obtained analogously in the reaction of thienothiophene 2, using an excess of ethylmagnesium bromide.²¹⁸

²⁶⁵ E. S. Gould, in "Mechanism and Structure in Organic Chemistry," p. 259. Holt, New York, 1959.

The 2-ethyl derivatives of thienothiophenes 1 and 2 form in high yields the corresponding monoacetoxymercury compounds which considerably differ in their melting-points and may be used for identification of the isomeric thienothiophenes.⁵⁷ Bisacetoxymercury compounds can be formed from 2,5-dialkyl thienothiophene 1. 2-Ethyl-5-methylthieno[2,3-*b*]thiophene with mercuric acetate in methanol produced the 3,4-bisacetoxymercury derivative.⁴⁴

n-Butyllithium metalation of thienothiophenes 1 and 2 (see Section IV,A) produces the corresponding 2-lithium derivatives.^{41,171,220} This reaction was used to introduce the ethylmercapto group into position 2 of thienothiophenes 1 and 2.²²⁰ Lithiation has also been used to separate 2,5-diethylthieno[2,3-*b*]thiophene (238) from the isomers contaminating it,²¹⁹ to replace the bromine in 3-bromothieno[2,3-*b*]thiophene and a hydrogen in thieno[2,3-*b*]thiophene (1) by a formyl group⁶⁸ and also for the preparation of 2,6-dibromothieno[3,2-*b*]thiophene from the 2,3,5-tribromo compound.¹⁷²

Carbonation of monolithio-thienothiophenes 1 and 2 formed by metalation with one equivalent of *n*-butyllithium furnished the 2-carboxylic acids in good yields.¹⁷¹ Two equivalents of *n*-butyllithium led to the 2,5-dicarboxylic acids. Metalation of the thienothiophene system at a β -position was not observed.

For competitive metalation of thiophene and the isomeric thienothiophenes 1 and 2, see Section IV,A and Table VII.

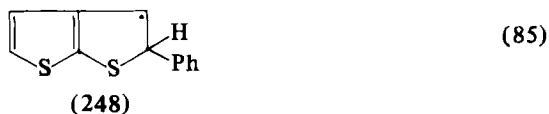
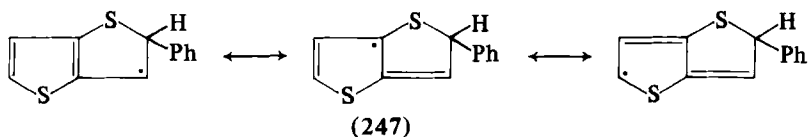
Metalation of thieno[3,4-*b*]thiophene (3) with one equivalent of *n*-butyllithium at -20° followed by dimethylformamide produced a mixture of 4-formyl (194) and 6-formylthieno[3,4-*b*]thiophene (195) in a 1:4 ratio, in contrast to the 7:3 ratio obtained by the Vilsmeier formylation of thienothiophene 3.¹⁶⁷

10. Reactions with Phenyl Radicals

From π -electron calculations, the following order of reactivity of the thienothiophenes 1–3 in free-radical substitution reactions was predicted: thieno[3,4-*b*]thiophene (3) > thiophene > thieno[3,2-*b*]thiophene (2) > thieno[2,3-*b*]thiophene (1), the most reactive positions being 2 and 5 in thienothiophenes 1 and 2, and 4 and 6 in thienothiophene 3.^{154,156}

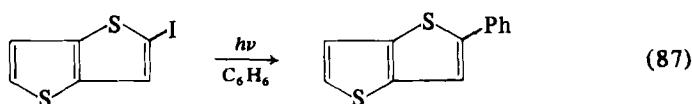
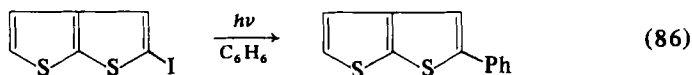
However, experimental studies of the effect upon thiophene or thienothiophenes 1 and 2 of phenyl radicals obtained by thermal decomposition of *N*-nitrosoacetanilide, or from aniline and amyl nitrite, demonstrated a somewhat different experimental order of reactivity: thieno[3,2-*b*]thiophene (2) > thiophene > thieno[2,3-*b*]thiophene (1).⁶⁹ It was also found that the phenyl radical preferentially attacks position 2

in thienothiophene 2 while the reactivities of positions 2 and 3 in thienothiophene 1 are almost equal. This difference in orientation of radical substitution was explained by the fact that the σ -complex (247) formed by attack at position 2 in thienothiophene 2 is stabilized by delocalization of the unpaired electron over all the molecule; this does not take place in the case of the corresponding σ -complex (248) of thienothiophene 1 formed by phenyl radical attack at position 2 [Eq. (85)].



The reduction of thienothiophene 2 with Na-K alloy produced a radical-anion^{187,188} (see Section III,D), and a radical-cation resulted from oxidation with AlCl_3 in nitromethane or SbCl_5 in methylene chloride²³⁷ (see Section IV,B,5). No such conversion was observed in the case of thienothiophene 1; this is explained by the extended conjugation throughout the thienothiophene 2 molecule, impossible in thienothiophene 1.

To confirm the structures of the products formed in the reaction between thienothiophenes 1 and 2 and phenyl radicals, the corresponding 2-phenyl- and 3-phenyl-substituted thienothiophenes 1 and 2 were synthesized by independent methods (see Section II,B). In addition, 2-phenyl-substituted thienothiophenes 1 and 2 were prepared by photolysis of the corresponding 2-iodo compounds,⁶⁹ under conditions previously used with the iodothiophenes²⁶⁶ [Eqs. (86), (87)].

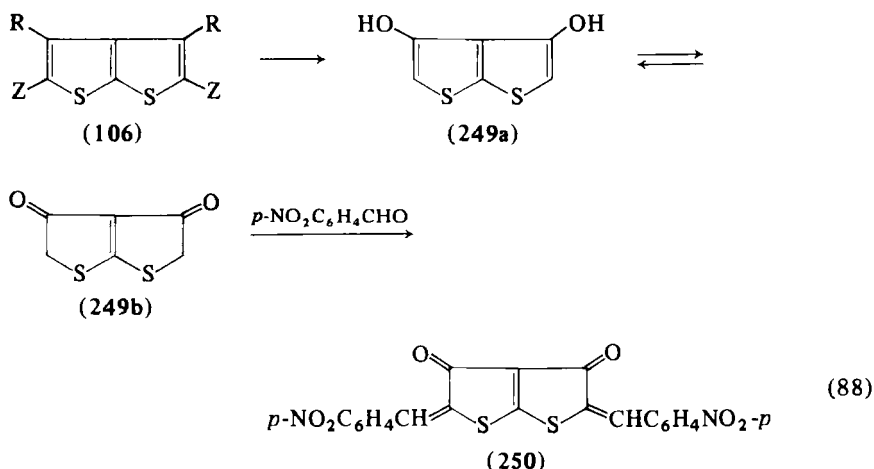


²⁶⁶ G. Martelli, P. Spagnolo, and M. Tiecco, *J. Chem. Soc. B*, 901 (1968).

11. Further Chemical Reactions and Possible Applications of the Isomeric Thienothiophenes

Thienothiophenes undergo the indophenine reaction with isatin (see Section III,I). Oster³ reported that thieno[2,3-*b*]thiophene (1) gave a green product with a ratio of isatin to thienothiophene 1:1, and a blue substance with the ratio of the initial substances 2:1. Steinkopf and Hempel²⁶⁷ could not obtain this blue substance; instead they isolated a brown material with the isatin to thienothiophene 1 ratio 2:3; at +50° they isolated a substance with the ratio 1:1; and at +70°, with ratio 1:2. Steinkopf and Petersdorf²⁶⁸ found that a reaction of 2-acetylthieno[2,3-*b*]thiophene with isatin produces 2- or 3-(2-thieno[2,3-*b*]thienyl) cinchoninic acid. The acid was decarboxylated to 2- or 3-(2-thieno[2,3-*b*]thienyl)quinoline (the site of quinoline group in thienothiophene 1 molecule was not established).

Dimethyl 3,4-dihydroxythieno[2,3-*b*]thiophene-2,5-dicarboxylate (106, R = OH, Z = CO₂Me),⁸⁴⁻⁸⁶ on heating with concentrated H₂SO₄ at 80° undergoes saponification and decarboxylation to form 3,4-dihydroxythieno[2,3-*b*]thiophene (249a). This, according to the IR spectrum, exists as the diketo form (249b), while the dicarboxylic acid (106, R = OH, Z = COOH) exists as the dienol⁸⁵ [Eq. (88)].

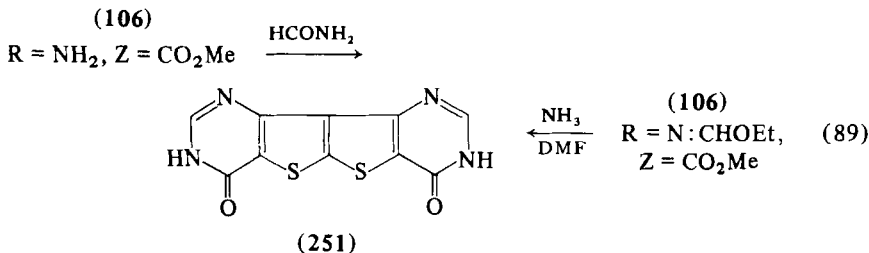


The diketothienothiophene (249b) can be condensed with aldehydes; thus *p*-nitrobenzaldehyde gives the 2,5-bis-*p*-nitrobenzylidene derivative (250).⁸⁵

²⁶⁷ W. Steinkopf and H. Hempel, *Ann.* **495**, 144 (1932).

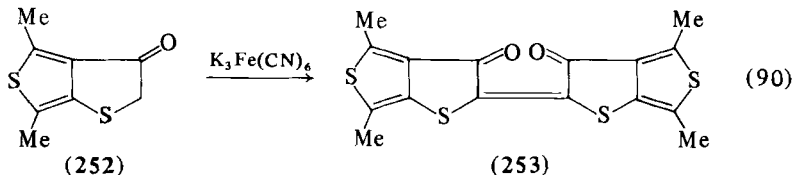
²⁶⁸ W. Steinkopf and H.-J. v. Petersdorff, *Ann.* **543**, 119 (1940).

Gompper and co-workers also showed that refluxing of dimethyl 3,4-diaminothieno[2,3-*b*]thiophene-2,5-dicarboxylate (**106**, $R = NH_2$, $Z = CO_2Me$) with formamide or treatment of the 3,4-bisethoxymethyl-enamino derivative with ammonia led to 3,4,7,8-tetrahydro-4,7-dioxo-pyrimido[5,4-*b'*]thieno[2,3-*b*]pyrimido[5,4-*b*]thiophene (**251**).⁸⁵ [Eq. (89)].

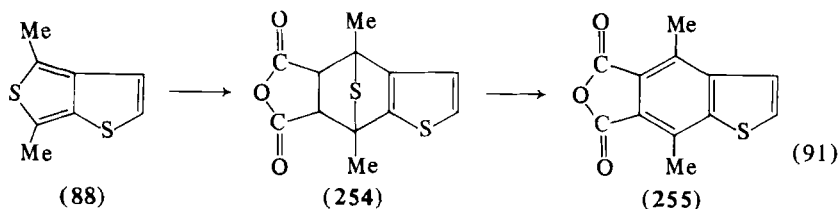


Substituted 3,4-diamino- (**107**) and 3,6-diaminothieno[3,2-*b*]thiophene (**108**) condense with aromatic aldehydes to form dyes.⁸⁸

Dann and Dimmling⁷⁵ showed that 2,3-dihydro-4,6-dimethylthieno[3,4-*b*]thiophen-3-one (**252**) was oxidized by alkaline ferricyanide to give a thioindigoid dye (**253**) [Eq. (90)] useful for dyeing cotton red with a

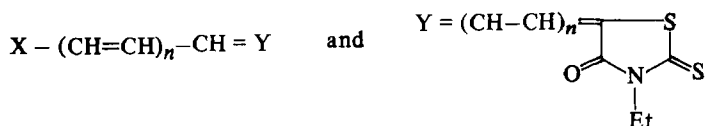


violet shade. 4,6-Dimethylthieno[3,4-*b*]thiophene (**88**) forms an adduct (**254**) with maleic anhydride which loses hydrogen sulfide at 160°, giving 4,7-dimethylbenzo[*b*]thiophene-5,6-dicarboxylic anhydride (**255**) [Eq. (91)].

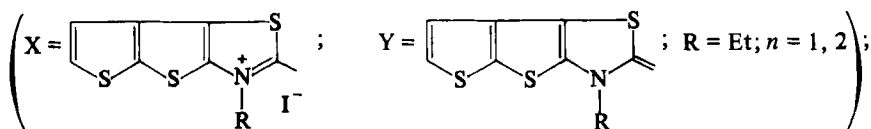


The ability to form adducts was also found in the so-called "non-classical" thienothiophene (**4**). As described above (see Section II,B), the sulfoxide of 4,6-dimethyl-1*H*,3*H*-thieno[3,4-*c*]thiophene (**143**) and 1,3,4,6-tetraphenylthieno[3,4-*c*]thiophene (**149**) react with *N*-phenylmaleimide to form *endo/exo* pairs of adducts: **144**, **145** and **150**, **151**.^{99,100}

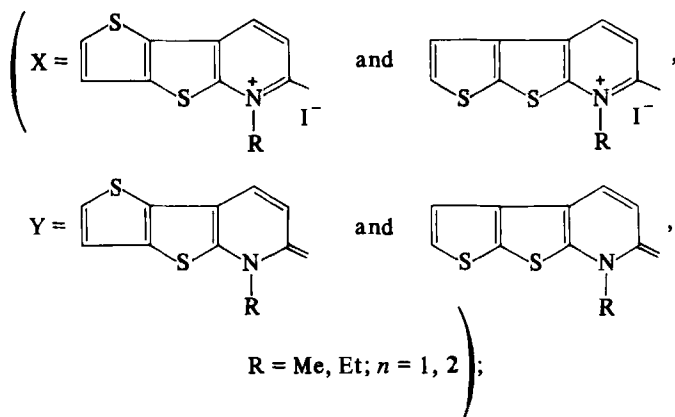
Zhiryakov and Abramenko,²⁶⁹⁻²⁷⁹ searching for optical sensitizers, synthesized polymethine dyes from thienothiophene 1 and 2 of type:



derived from quaternary salts of 2-methylthieno[2,3-*b*]thieno[2,3-*d*]-thiazole (209),^{271,276}



2-methylthieno[2,3-*b*]thieno[2,3-*b*]pyridine, (210) and 2-methylthieno[3,2-*b*]thieno[2,3-*b*]pyridine (211),^{270,272,277-279}



²⁶⁹ V. G. Zhiryakov, P. I. Abramenko, and N. I. Sennikova, *Avtorsk. Svid. SSSR*, No. 175819; *Byull. Izobret. Tovarnykh Znakov* 20, 122 (1965).

²⁷⁰ V. G. Zhiryakov, P. I. Abramenko, and G. F. Kurepina, *Avtorsk. Svid. SSSR* No. 177280; *Byull. Izobret. Tovarnykh Znakov* 24, 142 (1965).

²⁷¹ V. G. Zhiryakov, P. I. Abramenko, and G. F. Kurepina, *Avtorsk. Svid. SSSR* No. 177279; *Byull. Izobret. Tovarnykh Znakov* 24, 142 (1965).

²⁷² V. G. Zhiryakov, P. I. Abramenko, and G. F. Kurepina, *Avtorsk. Svid. SSSR* No. 179189; *Byull. Izobret. Tovarnykh Znakov* 4, 139 (1966).

²⁷³ P. I. Abramenko, *Dissert.*, Moscow, 1964.

²⁷⁴ V. G. Zhiryakov, *Dissert.*, Moscow, 1966.

²⁷⁵ V. G. Zhiryakov and P. I. Abramenko, *Khim. Geterotsikl. Soedin.*, 830 (1967).

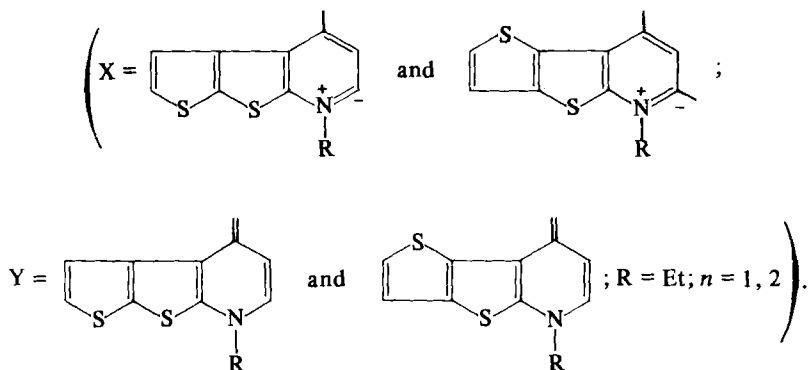
²⁷⁶ V. G. Zhiryakov and P. I. Abramenko, *Khim. Geterotsikl. Soedin.*, 480 (1969).

²⁷⁷ V. G. Zhiryakov and P. I. Abramenko, *Khim. Geterotsikl. Soedin.*, 491 (1969).

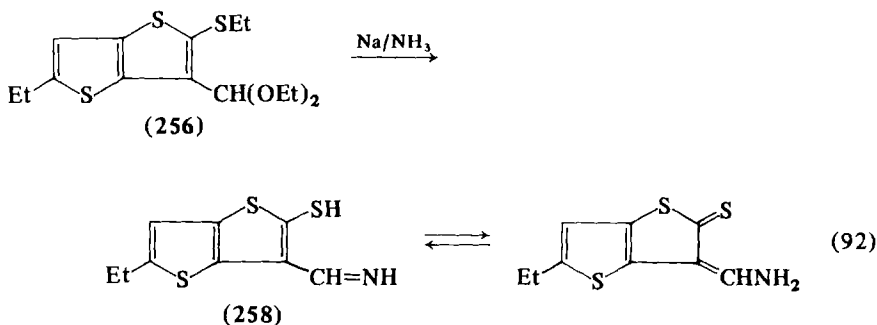
²⁷⁸ V. G. Zhiryakov and P. I. Abramenko, "Trudy Gosniikhimfotoproekt," Vol. 1, p. 18. Moscow, 1968.

²⁷⁹ V. G. Zhiryakov and P. I. Abramenko, "Trudy Gosniikhimfotoproekt," Vol. 1, p. 26. Moscow, 1968.

and 4-methylthieno[2,3-*b*]thieno[2,3-*b*]pyridine and 4-methylthieno[3,2-*b*]thieno[2,3-*b*]pyridine.^{269,275,278}

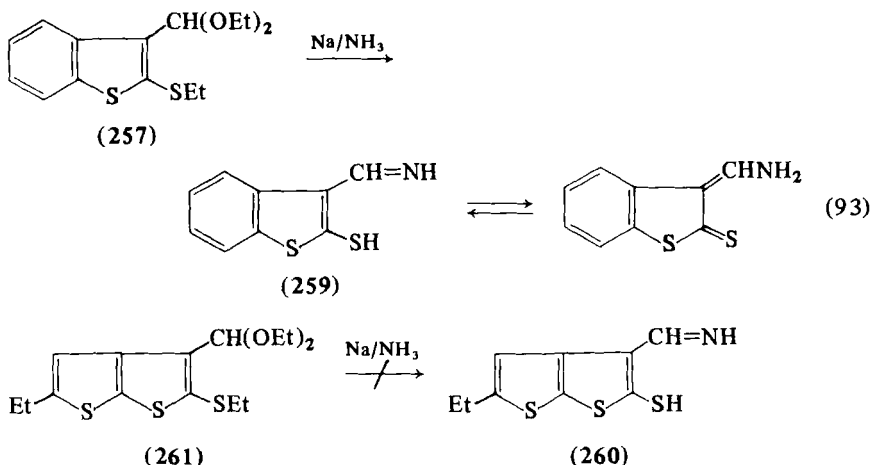


There is at present a growing interest in complexing compounds containing sulfur, selenium and tellurium as donor atoms.²⁸⁰ Compounds of this kind are the *o*-mercaptoaldimines of the thiophene series synthesized by Gol'dfarb and Kalick⁷⁰ (see Section II,B). In the condensed systems, the treatment of 5-ethyl-2-ethylthio-3-formylthieno[3,2-*b*]thiophene acetal (256) and 2-ethylthio-3-formylbenzo[*b*]thiophene acetal (257) with sodium in liquid ammonia gave good yields of the 3-iminomethyl-2-mercapto compounds 258 and 259, respectively^{220,281} [Eqs. (92), (93)]. An attempt to obtain a similar mercaptoaldimine (260) from 5-ethyl-2-ethylthio-3-formylthieno[2,3-*b*]thiophene acetal (261) was unsuccessful, illustrating the difference in reactivities of thienothiophenes 1 and 2.

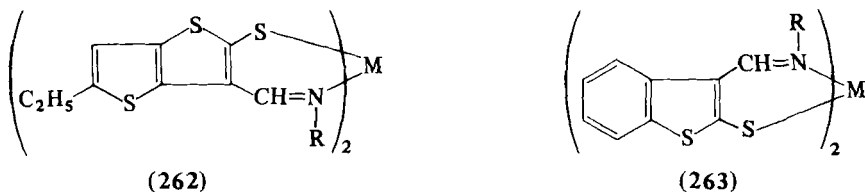


²⁸⁰ S. E. Livingstone, *Quart. Rev. Chem. Soc.* **19**, 386 (1965).

²⁸¹ Ya. L. Gol'dfarb, S. A. Ozolin and V. P. Litvinov, *Avtorsk. Svid. SSSR No. 201427* (1966); *Bull. Izobret. Tovarnykh Znakov* **18**, 40 (1967).



Mercaptoaldimes 258 and 259 form Schiff bases with amines which are of considerable interest as complexing agents, producing chelates 262 and 263 with metal salts.^{220,281}



M = Zn, Ni, Cu, etc.

Appendix

The following references relating to thienothiophene chemistry appeared in the course of the preparation of this review. *Chemical Abstracts* 80 and issues 1-15, 81 (1974) have been covered.

1. D. M. Altwein, Derivatives of 2-aminothieno[2,3-*b*]thiophene and synthesis of 3-methylthieno[2,3-*b*]thiophene. Ph.D. Thesis, University of Washington (1973); *Diss. Abstr. B* 34, 1441 (1973).
2. M. A. Sprecker, Nonclassical condensed thiophenes. Ph.D. Thesis, University of Pennsylvania (1973); *Diss. Abstr. B* 34, 4299 (1974).
3. W. B. Wright, N-(Aminodialkyl)thieno[3,2-*b*]thiophene-2-carboxamides. *U.S. Patent* 3,733,322 (1973); *CA* 79, 18688 (1973).
4. K. Gewald and J. Schael, Reaction of 3-thiacyclopentanone with cyanoacetate and sulfur. *J. Prakt. Chem.* 315, 39 (1973); *Synthesis*, 695 (1973).

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11. I. Ya. Kvitko, N. B. Sokolova, and L. S. Efros, Synthesis of thieno[2,3-*b*] and selenopheno[2,3-*b*]furan. *Khim. Geterotsikl. Soedin.*, 715 (1973).
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13. P. Fournari and P. Meunier, Heterocyclic series. XXII. Synthesis of bromo-thieno[2,3-*b*]thiophenes. *Bull. Soc. Chim. Fr.* 583 (1974).
14. P. Meunier and P. Fournari, Heterocyclic series, XXIII. Synthesis of iodothieno[2,3-*b*]thiophenes. *Bull. Soc. Chim. Fr.* 587 (1974).
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19. S. Gronowitz, T. Frejd, and A.-B. Hörnfeldt, Structure of the high-melting selenophthene. *Chem. Scripta* 5, 236 (1974).
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1,2,3-Triazines

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The chemistry of the 1,2,3-triazines was reviewed by Erickson¹ in 1956 and by Horowitz² in 1961. Interest in this ring system has,

¹ J. G. Erickson, in "The Chemistry of Heterocyclic Compounds" (A. Weissberger, ed.), Vol. 10, Chapter 1. Wiley (Interscience), New York, 1956.

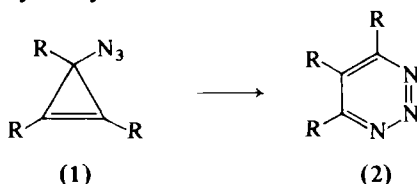
² J. P. Horowitz in "Heterocyclic Compounds" (R. C. Elderfield, ed.), Vol. VII, Chapter 9. Wiley, New York, 1961.

however, increased substantially during the last fifteen years, largely as a result of the wide range of biological activity associated with many derivatives of 1,2,3-benzotriazin-4(3*H*)-one, and an attempt has been made in the present review to provide a comprehensive survey of developments in 1,2,3-triazine chemistry from 1960 through to the beginning of 1974. Reference is made to results published prior to 1960 in most cases only where data available from more recent investigations have resulted in the extension, elucidation, clarification, or contradiction of earlier methods or conclusions.

1. 1,2,3-Triazines

1,2,3-Triazine has not yet been prepared, and until fairly recently there were no well-documented examples of monocyclic 1,2,3-triazine derivatives. Early estimates of the potential degree of stability of 1,2,3-triazine were made on the basis of the theoretical resonance energy: the results obtained indicated a delocalization energy of about 25 kcal/mole, which implies that the ring system should be reasonably stable and certainly amenable to synthesis.³ Many other related molecular orbital (MO) calculations have been carried out on similar systems more recently.⁴⁻¹⁰

The first derivative of 1,2,3-triazine to be prepared, the triphenyl compound (2, R = Ph), was obtained in 1960 by thermolysis of 1,2,3-triphenylcyclopropenyl azide (1, R = Ph).¹¹ The physical and spectral (IR and UV) properties of 2 were consistent with the assigned structure, and the presence of three contiguous carbon atoms was demonstrated by hydrolysis experiments, which resulted in formation of 1,2,3-triphenylbutane-1,3-dione. Photolysis of 2 gave a mixture of nitrogen, benzonitrile, and diphenylacetylene.



³ A. Maccoll, *J. Chem. Soc.*, 670 (1946).

⁴ G. Favini, I. Vandoni, and M. Simonetta, *Theor. Chim. Acta* 3, 45 (1965).

⁵ M. J. S. Dewar and G. J. Gleicher, *J. Chem. Phys.* 44, 759 (1966).

⁶ G. Favini, I. Vandoni, and M. Simonetta, *Theor. Chim. Acta* 3, 418 (1965).

⁷ P. Balayn and G. Mesnard, *Cah. Phys.* 20, 71 (1966) [*CA* 66, 10483 (1967)].

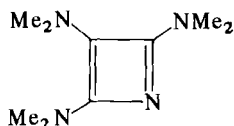
⁸ G. W. Pukanic, D. R. Forshey, J. D. Wegener, and J. B. Greenshields, *Theor. Chim. Acta* 10, 240 (1968).

⁹ M. S. de Giambiagi and M. Giambiagi, *J. Chim. Phys.* 64, 880 (1967).

¹⁰ M. S. de Giambiagi and M. Giambiagi, *Theor. Chim. Acta* 8, 341 (1967).

¹¹ E. A. Chandross and G. Smolinsky, *Tetrahedron Lett.*, 19 (1960).

Thermolytic rearrangement of 1,2,3-trisubstituted cyclopropenyl azides constitutes the only proven method at present for the preparation of monocyclic 1,2,3-triazines, and both the generality and validity of the procedure have been established. Thus, a substantial number of derivatives of the type 2, R = alkyl, aryl, have now been prepared,^{12,13} and X-ray crystallographic analysis has confirmed the structures of the products (see Section II, D, 2).¹⁴ Thermolysis of triarylcyclopropenyl



(3)

azides in which the three aryl substituents are not identical leads, as expected, to mixtures of isomeric triazines.¹³ More recently, this general method has been extended to the synthesis of 2, R = NMe₂, pyrolysis of which was shown to result in formation of the interesting, theoretically antiaromatic, compound 3.¹⁵ Preparation of 1,2,3-triazines by other methods has been claimed,¹⁶⁻²⁷ but the procedures used have not yet

¹² G. L. Closs and A. M. Harrison, *J. Org. Chem.* **37**, 1051 (1972).

¹³ H. Neunhöffer, H.-D. Vötter, and H. Ohl, *Chem. Ber.* **105**, 3695 (1972).

¹⁴ E. Oeser and L. Schiele, *Chem. Ber.* **105**, 3704 (1972).

¹⁵ G. Seybold, U. Jersak, and R. Gompper, *Angew. Chem., Int. Ed. Engl.* **12**, 847 (1973).

¹⁶ T. Sato, *J. Org. Chem.* **24**, 963 (1959).

¹⁷ A. K. Mindyuk, V. P. Koval, I. I. Vasilenko, and Yu. I. Babei, *Fiz.-Khim. Mekh. Mater.* **7**, 104 (1971) [*CA* **75**, 120581 (1971)].

¹⁸ V. D. Fateev, S. A. Balezin, and N. G. Klyuchnikov, *Uch. Zap., Mosk. Gos. Pedagog. Inst.* **303**, 181 (1969) [*CA* **77**, 37985 (1972)].

¹⁹ G. L. Nemchaninova and N. G. Klyuchinov, *Uch. Zap., Mosk. Gos. Pedagog. Inst.* **340**, 79 (1971) [*CA* **77**, 42449 (1972)].

²⁰ S. A. Balezin, N. O. Podobaev, and A. M. Solok, *Uch. Zap., Mosk. Gos. Pedagog. Inst.* **303**, 128 (1969) [*CA* **77**, 37857 (1972)].

²¹ V. I. Rodionova and L. Z. Bondarenko, *Uch. Zap., Mosk. Gos. Pedagog. Inst.* **303**, 109 (1969) [*CA* **77**, 37859 (1972)].

²² E. S. Bulavina and N. I. Podabaev, *Uch. Zap., Mosk. Gos. Pedagog. Inst.* **340**, 150 (1971) [*CA* **77**, 51565 (1972)].

²³ S. A. Balezin, V. I. Rodionova, and E. S. Bulavina, *Uch. Zap., Mosk. Gos. Pedagog. Inst.* **303**, 175 (1969) [*CA* **77**, 37978 (1972)].

²⁴ F. B. Glikina, E. S. Bulavina, and N. I. Podabaev, *Uch. Zap., Mosk. Gos. Pedagog. Inst.* **303**, 190 (1969) [*CA* **77**, 37983 (1972)].

²⁵ V. A. Mukhin and B. I. Chernov, *Nauch. Tr. Omsk. Inst. Zheleznodorozh. Transp.* **124**, 38 (1971) [*CA* **78**, 127591 (1973)].

²⁶ I. K. Chernegova, V. K. Suprunchurk, and I. D. Vdovenko, *Korroz. Zashch. Metal. Mater.*, 55 (1972) [*CA* **78**, 114585 (1973)].

²⁷ G. P. Maitak and N. A. Ishchenko, *Korroz. Zashch. Metal. Mater.*, 49 (1972) [*CA* **78**, 78834 (1973)].

been substantiated, and in all cases structures more probable than 1,2,3-triazines can be advanced for the reaction products.

Little is known as yet of the chemistry of the monocyclic 1,2,3-triazines. The only reactions that have been reported are hydrolysis to substituted butane-1,3-diones, photolytic decomposition to acetylenes, nitriles, and nitrogen, and high temperature (250°) thermolysis, which leads to loss of nitrogen and formation of the corresponding diarylindenone imines. The structures of the latter compounds were confirmed on the basis of their physical properties and by hydrolysis to the corresponding known diarylindenones.²⁸

All the well-characterized 1,2,3-triazine derivatives are stable, high-melting solids. The 4,5,6-triaryl derivatives show UV maxima in the range 259–286 nm ($\log \epsilon = 4.09\text{--}4.42$),¹³ 4,5-diphenyl-1,2,3-triazine has λ_{\max} at 251 nm,¹³ while the 4,5,6-trimethyl derivative shows two maxima at 217 nm ($\log \epsilon = 3.63$) and 278 nm ($\log \epsilon = 2.79$).¹² Mass spectral studies indicate that fragmentation takes place in an identical fashion to that observed during photochemical decomposition, i.e., with production of acetylenes, nitriles, and nitrogen.¹³

The structure of 2, $R = p\text{-MeOC}_6\text{H}_4$, has been confirmed by X-ray analysis,¹⁴ and the data obtained are of interest in comparison to those reported for 1,2,3-benzotriazin-4(3*H*)-one (see p. 262). Thus, in contrast to the bond lengths found for this latter compound, the $\text{N}_1\text{—N}_2$ bond length in 2, $R = p\text{-MeOC}_6\text{H}_4$, was found to be 1.314 Å (cf 1.26 Å for a “pure” $\text{N}=\text{N}$ double bond); the $\text{N}_2\text{—N}_3$ bond length was 1.319 Å (cf 1.46 Å for a N—N single bond); and $\text{N}_3\text{—C}_4$ was 1.368 Å (cf 1.45 Å for a $\text{C}=\text{N}$ double bond). This is a very unexpected set of bond lengths—and, by extrapolation, unexpected bond orders—and consequently it can be anticipated that further study of the properties of simple 1,2,3-triazine derivatives may well reveal some unusual chemistry.

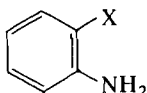
II. 1,2,3-Benzotriazines and Other Condensed 1,2,3-Triazines

A. SYNTHESIS

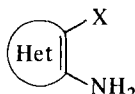
There are relatively few methods available for the preparation of condensed 1,2,3-triazines. By far the most commonly employed procedure is diazotization of a suitably ortho-substituted aniline (4) or amino-substituted heterocycle of the type 5, and examination of the different X substituents which have been used successfully in this synthesis reveals

²⁸ H. Neunhöffer, H.-D. Vötter, and M. Gais-Mutterer, *Tetrahedron Lett.*, 219 (1973).

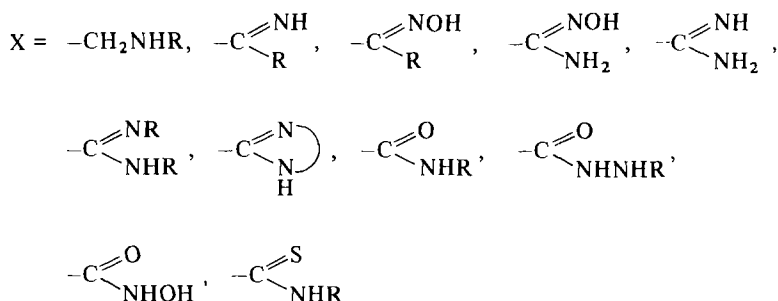
the generality of the method. Almost all the other methods that have been used for the construction of the heterocyclic ring in condensed 1,2,3-triazines are very much less general than the above classical procedure; most have been explored only briefly as routes to specific compounds, or types of compounds, and the scope and limitations of these methods have apparently been thoroughly investigated in only one instance (see p. 231). In addition to methods that involve total constructions, in which the functional groups in preformed benzo-1,2,3-triazine following discussion of certain types of substituent transformation reactions, in which the functional groups in preformed benzo-1,2,3-triazine derivatives are converted into different functional groups by use of techniques that are standard in synthetic heterocyclic chemistry.



(4)



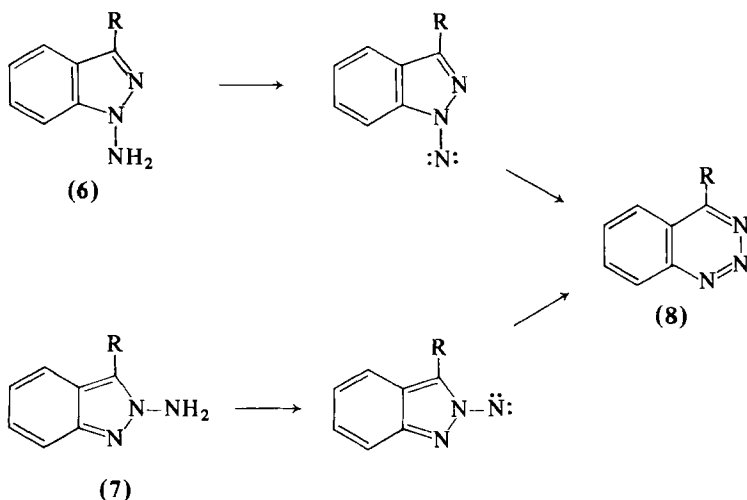
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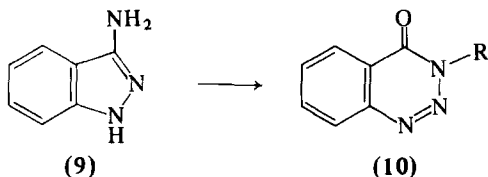
1. 1,2,3-Benzotriazine, 4-Alkyl- and 4-Aryl-1,2,3-benzotriazines

Lead tetraacetate oxidation of 3-substituted 1- and 2-aminoindazoles **6** and **7**, has been shown by Rees to result in rapid and almost quantitative conversion into 4-substituted 1,2,3-benzotriazines (**8**, R = Me, OMe, Ph).²⁹ 1,2,3-Benzotriazine (**8**, R = H) was prepared similarly, and for the first time, by carefully controlled oxidation of either 1- or 2-aminoindazole (**6**, **7**, R = H). These remarkable ring expansion reactions, which apparently proceed via the formation of intermediate nitrenes, appear to be a direct and logical extension of original work by Bamberger and Goldberger in 1898 on the oxidative ring expansion of

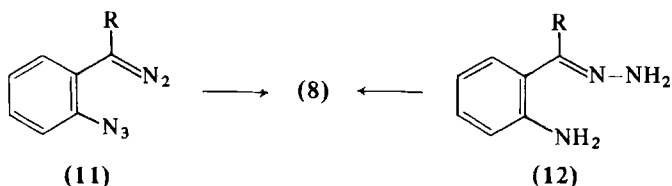
²⁹ D. J. C. Adams, S. Bradbury, D. C. Horwell, M. Keating, C. W. Rees, and R. C. Storr, *Chem. Commun.*, 828 (1971).



3-aminoindazole (9) to 1,2,3-benzotriazin-4(3*H*)-one (10, R = H) (see Section II, A, 4).^{30,31} The mechanism of this latter conversion is not known with certainty.³²



Alternative procedures for the preparation of 4-alkyl- and 4-aryl-1,2,3-benzotriazines have also been investigated by Rees.³³ Thus, the diazoazide (11) undergoes smooth decomposition in refluxing benzene to give 4-methyl-1,2,3-benzotriazine (8, R = Me) in 70% yield. Oxidation of the *o*-aminohydrazones (12, R = Me, Ph, *p*-MeOC₆H₄) with lead tetraacetate also gives the corresponding triazines (8) in moderate yield,

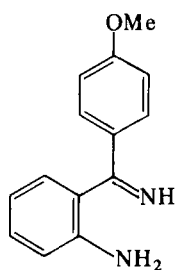


³⁰ E. Bamberger and A. von Goldberger, *Chem. Ber.* **31**, 2636 (1898).

³¹ E. Bamberger, *Liebigs Ann. Chem.* **305**, 333, 359 (1899).

³² But see p. 16 in Erickson.¹

³³ S. Bradbury, M. Keating, C. W. Rees, and R. C. Storr, *Chem. Commun.*, 827 (1971).

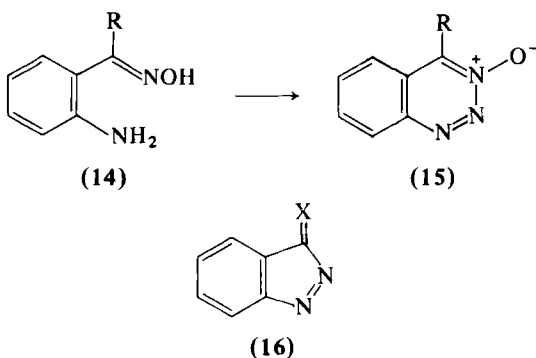


(13)

presumably by initial conversion into the corresponding *o*-aminodiazo compounds, cyclization to the dihydrotriazines, and, finally, oxidation to the aromatic systems. 4-(*p*-Methoxyphenyl)-1,2,3-benzotriazine (8, R = *p*-MeOC₆H₄) has also been prepared by diazotization of the imine 13.³⁴

2. Condensed 1,2,3-Triazine 3-Oxides

Direct oxidation of condensed 1,2,3-triazines to N-oxides has not been studied in detail, and the feasibility of such methods has been rigorously established in only a single instance (see Section II, C, 2). With the exception of the 1,2,3-triazinium betaine N(1)-oxides, which are discussed separately, all the remaining known 1,2,3-triazine N-oxides, which are 3-oxides, have been prepared by diazotization of appropriate precursors. Thus, diazotization of *o*-aminophenylketoximes (14, R = Me, Ph) gives the corresponding 4-substituted 1,2,3-benzotriazine 3-oxides (15) directly.³⁵⁻³⁸ Formulation of these products as triazine N-



³⁴ A. J. Nunn and K. Schofield, *J. Chem. Soc.*, 716 (1953).

³⁵ E. Bamberger and M. Weiler, *J. Prakt. Chem.* **58**, 333 (1898).

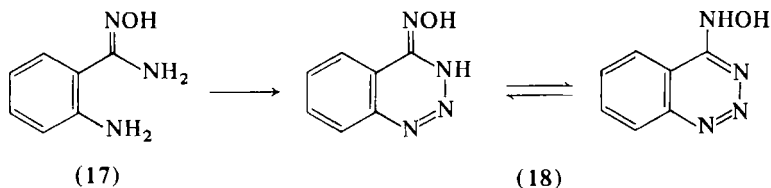
³⁶ E. Bamberger and E. Demuth, *Chem. Ber.* **34**, 1309 (1901).

³⁷ C. Sumuleanu, *Ann. Sci. Univ. Jassy* **2**, 131 (1903). *Chem. Zentralbl.* **11**, 31 (1903).

³⁸ J. Meisenheimer, O. Senn, and P. Zimmermann, *Chem. Ber.* **60**, 1736 (1927).

oxides was based entirely on chemical evidence: reaction of **15** with acids (H_2SO_4 , $\text{PCl}_3/\text{PCl}_5$) results in facile cleavage of the heterocyclic ring and formation of *o*-azidophenylketones; treatment with hydroxylamine leads to regeneration of **14**; reduction gives 3-methylindazole (for reduction, see Section II, C, 2). Diazotization of *o*-aminobenzaldoxime (**14**, $\text{R} = \text{H}$) gives a product which was formulated as 3-oximinobenzotriazole (**16**, $\text{X} = \text{NOH}$).³⁶ The structurally related indazolones (**16**, $\text{X} = \text{O}$) are known, however, to be extremely unstable and to decompose readily in the presence of nucleophiles with loss of nitrogen.³⁹ Consequently, it is highly probable that the relatively stable product obtained from diazotization of **14**, $\text{R} = \text{H}$, is in fact 1,2,3-benzotriazine 3-oxide (**15**, $\text{R} = \text{H}$).

In 1896 Pinnow and Sämman reported that diazotization of *o*-aminobenzamidoxime (**17**) gave the amphoteric compound (**18**) as the sole reaction product.⁴⁰ Structural assignment was based on chemical evidence which was erroneously interpreted, and reinvestigation of this reaction by Parnell has established that the correct structure for this



product is **20**.⁴¹ Pinnow and Sämman had reported that reduction of (**18**) gave 1,2-dihydro-1,2,3-benzotriazine (**19**); subsequent repetition of this work revealed that the reduction product was not **19**, but was "*o*-cyano-phenylhydrazine,"⁴² which does not exist as such but is simply 3-aminobenzotriazole (**9**).^{43,44} Parnell, in a careful reexamination of the whole problem, prepared a genuine sample of **18** by nucleophilic displacement of hydrogen sulfide from 1,2,3-benzotriazine-4(3*H*)-thione with hydroxylamine, showed that **18** was different from the product obtained by the method of Pinnow and Sämman, and that the structure of this last compound was **20**. It follows from Parnell's study that the "4-hydroxylamino" 1,2,3-benzotriazine derivatives prepared by Grundmann and Ulrich⁴⁵ have also been assigned incorrect structures and are in fact derivatives of 4-amino-1,2,3-benzotriazine 3-oxide.

³⁹ J. Adamson, D. L. Forster, T. L. Gilchrist, and C. W. Rees, *J. Chem. Soc. C*, 981 (1971).

⁴⁰ J. Pinnow and C. Sämman, *Chem. Ber.* **29**, 623 (1896).

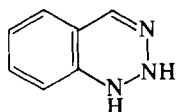
⁴¹ E. W. Parnell, *J. Chem. Soc.*, 4930 (1961).

⁴² G. Heller, *J. Prakt. Chem.* **111**, 1 (1925).

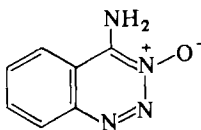
⁴³ M. A. Aron and J. A. Elvidge, *Chem. Ind. (London)*, 1234 (1958).

⁴⁴ F. C. Cooper, *J. Chem. Soc.*, 4212 (1958).

⁴⁵ C. Grundmann and H. Ulrich, *J. Org. Chem.* **24**, 272 (1959).

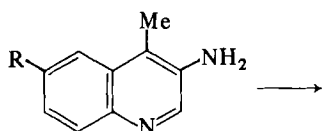


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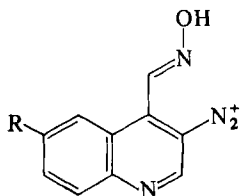


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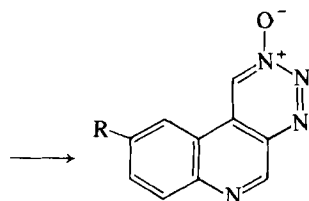
The diazotization procedure for the preparation of condensed 1,2,3-triazine 3-oxides has been extended to certain heterocyclic systems in which there is an amino group beta to a ring nitrogen atom and a methyl group alpha or gamma to the same atom. Thus, diazotization of the 3-amino-4-methylquinolines (21, R = H, Cl) in strong hydrochloric acid gives the N-oxides (23, R = H, Cl) in good yield, presumably via oximation of the activated methyl group and cyclization of the intermediate diazonium salt (22).⁴⁶ Interestingly, this type of reaction was



(21)



(22)



(23)

discovered by Behrend as long ago as 1888, although the results were misinterpreted at the time and for almost a hundred years afterward. Behrend reported that treatment of 6-methyl-5-aminouracil (24, R = H) with nitrous acid gave 25.⁴⁷ Rose, in 1952, discounted this structure and reformulated the product as the pyrimido-oxadiazole (26).⁴⁸ In 1963, however, Papesch and Dodson established unambiguously that both 25 and 26 were incorrect, and that the structures of the products obtained from the diazotization of 24, R = Me, Et were in fact 27, R = Me, Et,⁴⁹ a result subsequently confirmed by Davis *et al.* in 1970 for the conversion 24, R = H → 27, R = H.⁵⁰

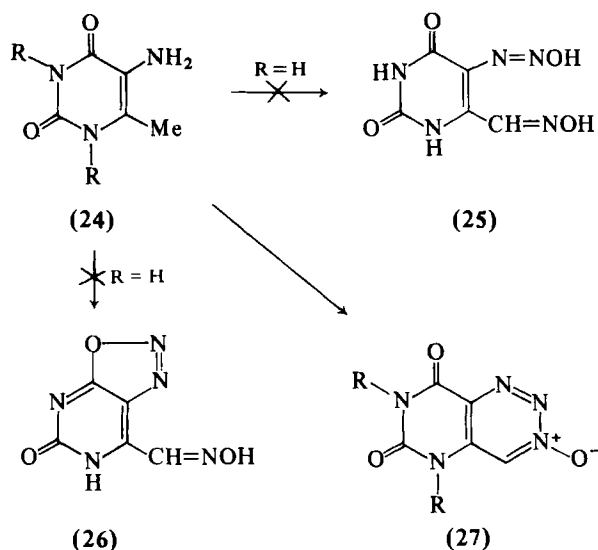
⁴⁶ D. W. Ockenden and K. Schofield, *J. Chem. Soc.*, 1915 (1953).

⁴⁷ R. Behrend, *Liebigs Ann. Chem.* 245, 213 (1888).

⁴⁸ F. L. Rose, *J. Chem. Soc.*, 3448 (1952).

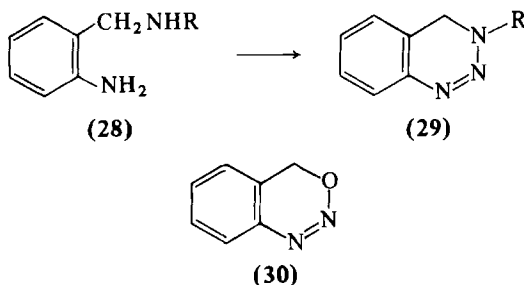
⁴⁹ V. Papesch and R. M. Dodson, *J. Org. Chem.* 28, 1329 (1963).

⁵⁰ J. C. Davis, H. H. Ballard, and J. W. Jones, *J. Heterocycl. Chem.* 7, 405 (1970).



3. Condensed 3,4-Dihydro-1,2,3-triazines

Diazotization of substituted *o*-aminobenzylamines of the type **28**, R = alkyl, aryl, acyl, gives 3-substituted 3,4-dihydrobenzo-1,2,3-triazines (**29**).⁵¹⁻⁵⁹ *o*-Aminobenzylamine does not react similarly, but gives a product to which structure **30** has been assigned.⁵⁴ Treatment of 1,8-diaminonaphthalene (**31**, R = H) with nitrous acid gives naphtho[1,8-



⁵¹ M. Busch, *J. Prakt. Chem.* **51**, 257 (1895).

⁵² M. Busch, *J. Prakt. Chem.* **52**, 373 (1895).

⁵³ M. Busch, *J. Prakt. Chem.* **55**, 356 (1897).

⁵⁴ M. Busch, *J. Prakt. Chem.* **51**, 113 (1895).

⁵⁵ M. Busch, *Chem. Ber.* **25**, 445 (1892).

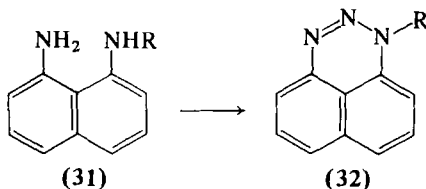
⁵⁶ R. von Walther and R. Bamberg, *J. Prakt. Chem.* **71**, 153 (1905).

⁵⁷ S. Reich and M. Ghazarian, *Bull. Soc. Chim. Fr.*, 261 (1916).

⁵⁸ G. T. Morgan and F. M. G. Micklethwait, *J. Chem. Soc.*, 1158 (1906).

⁵⁹ G. T. Morgan and F. M. G. Micklethwait, *J. Chem. Soc.*, 602 (1908).

de]triazine (32, R = H) in good yield,^{60,61} and substituted 1,8-diaminonaphthalenes (32, R = Ph, SO₂Ph) react similarly.^{62,63} Many substituted triazines of the type 32, R = alkyl, aryl, have also been prepared by base-catalyzed alkylation and arylation of 32, R = H (for details, see Section II, C, 3).⁶⁴



4. Condensed 1,2,3-Triazine-4(3H)-ones and 1,2,3-Triazine-4(3H)-thiones

There are two general ring syntheses available for the preparation of 3-substituted 1,2,3-benzotriazin-4(3H)-ones, namely, (i) diazotization of anthranilamide and its derivatives and (ii) cyclization of 1-alkyl- or 1-aryl-3-(*o*-carbalkoxy)triazenes, and both reactions have been studied in considerable detail. 3-Substituted 1,2,3-benzotriazin-4(3H)-ones have also been obtained by alkylation and acylation of 1,2,3-benzotriazin-4-one; these last reactions are discussed separately (see Section II, C, 3).

Diazotization of anthranilamide and its derivatives is the most common and widely exploited reaction for the preparation of 1,2,3-benzotriazine derivatives. The reasons for this are 3-fold: (i) many nuclear substituted anthranilic acid derivatives are readily available; (ii) the diazotization reactions generally proceed smoothly and in high yield, and the product triazinones are usually very stable and easily handled; and (iii) many 3-substituted 1,2,3-benzotriazin-4(3H)-ones have been found to possess a wide range of pronounced pharmacological activity, while others undergo a number of very interesting chemical transformations, and hence a very large number of these compounds have been prepared.

Diazotization of anthranilamide gives 1,2,3-benzotriazin-4(3H)-one (10, R = H) in good yield.⁶⁵ Treatment of isoatoic diamide (33) with nitrous acid also gives 10 (R = H),⁶⁶ and a great many 3-substituted

⁶⁰ A. de Aguiar, *Chem. Ber.* **7**, 306 (1874).

⁶¹ H. Waldmann and S. Back, *Liebigs Ann. Chem.* **545**, 52 (1940).

⁶² F. Sachs, *Liebigs Ann. Chem.* **365**, 53 (1909).

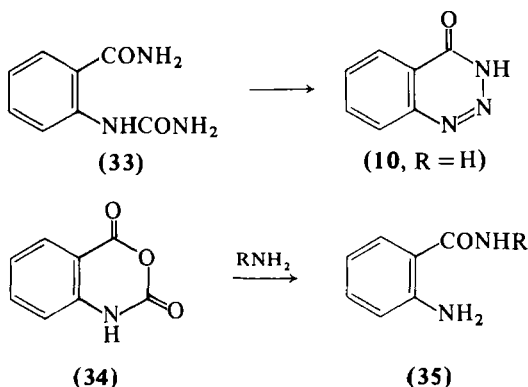
⁶³ G. T. Morgan and F. M. G. Micklethwait, *J. Chem. Soc.*, **4** (1906).

⁶⁴ M. J. Perkins, *J. Chem. Soc.*, 3005 (1964).

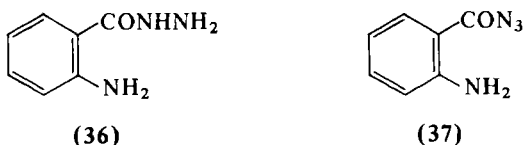
⁶⁵ H. Finger, *J. Prakt. Chem.* **37**, 431 (1888).

⁶⁶ G. Jacini, *Gazz. Chem. Ital.* **77**, 308 (1947).

derivatives (**10**, R = alkyl, aryl) have been prepared similarly from the corresponding anthranilamides (**35**),^{30,31,67-69} which are readily available from isatoic anhydride (**34**) by reaction with amines.⁷⁰ Diazotization of anthranilic hydrazide (**36**) is, however, a more complex reaction.^{71,72}



Treatment of **36** with nitrous acid in dilute acetic acid gives a mixture of anthranilazine (**37**) and 3-amino-1,2,3-benzotriazin-4(3*H*)-one (**10**, R = NH₂).⁷² When the same reaction is carried out in dilute hydrochloric acid, the sole product formed initially with one mole equivalent of nitrous acid is **10**, R = NH₂, but this readily reacts further to give **10**, R = H.⁷² Diazotization of acetophenone anthranilhydrazone followed by mild acid hydrolysis is a superior route to **10**, R = NH₂, and gives a much purer product.^{39,73} 1,2,3-Benzotriazine-4(3*H*)-thione (**39**, R = H) and the 3-substituted derivatives (**39**) are readily available by diazotization of thioanthranilamide (**38**, R = H) and its derivatives.⁷⁴



⁶⁷ A. Weddige and H. Finger, *J. Prakt. Chem.* **35**, 262 (1887).

⁶⁸ H. Kratz, *J. Prakt. Chem.* **52**, 210 (1896).

⁶⁹ S. von Niementowski, *Chem. Ber.* **21**, 1534 (1888).

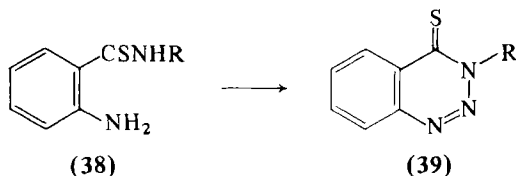
⁷⁰ See, e.g., Adamson *et al.*,³⁹ and S. M. Gadeker and E. Ross, *J. Org. Chem.* **26**, 613 (1961).

⁷¹ H. Finger, *J. Prakt. Chem.* **48**, 92 (1893).

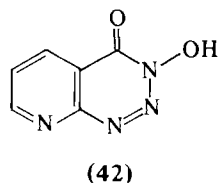
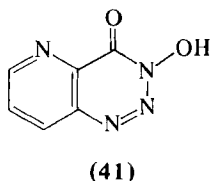
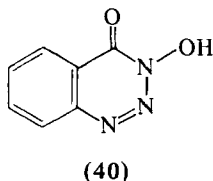
⁷² G. Heller and A. Siller, *J. Prakt. Chem.* **116**, 9 (1927).

⁷³ G. Heller, *J. Prakt. Chem.* **111**, 36 (1925).

⁷⁴ A. Reissert and F. Grube, *Chem. Ber.* **42**, 3710 (1909).



Acylhydrazides of anthranilic acid (**35**, $R = \text{NHCOR}^1$) give 3-acylamino-1,2,3-benzotriazin-4(3*H*)-ones (**10**, $R = \text{NHCOR}^1$) on treatment with nitrous acid.⁷³ The triazine hydroxamic acid (**40**) and its benzo-substituted derivatives are available by diazotization of the corresponding *o*-aminobenzohydroxamic acids.⁷⁵ The pyrido[2,3-*e*]triazine analog (**41**) was prepared similarly from 3-aminoisonicotinohydroxamic acid, but the isomeric 2-aminonicotinohydroxamic acid failed to react under the same conditions to give **42**.⁷⁵



The diazotization procedure has been applied to the preparation of a wide range of condensed 1,2,3-triazinones, for example, the bicyclic systems **43**,⁷⁶ **44**,⁷⁷ **45**,⁷⁸ **46**,⁷⁹ **47**,⁸⁰ **48**,⁸¹ and **49**⁸¹ and the tricyclic systems **50**,^{39,82,83} **51**,⁸⁴ and **52**.⁸⁵

1-Aryl-3-(*o*-carbalkoxyphenyl)triazenes (**53**, $R = \text{aryl}$) are readily accessible by treatment of diazotized anthranilic esters with substituted anilines and are reasonably stable. They can, for instance, be crystallized unchanged from 95% ethanol, but undergo facile, high-yield ring closure to the 3-aryl-1,2,3-benzotriazin-4(3*H*)-ones (**10**, $R = \text{aryl}$) when heated in ethanol containing either substantial amounts of water

⁷⁵ D. Harrison and A. C. B. Smith, *J. Chem. Soc.*, 2157 (1960).

⁷⁶ H. Weidel and L. Niemilowicz, *Monatsh. Chem.* **16**, 746 (1895).

⁷⁷ R. Justino and R. Fusco, *Gazz. Chem. Ital.* **68**, 59 (1938).

⁷⁸ D. W. Woolley and E. Shaw, *J. Biol. Chem.* **189**, 401 (1951).

⁷⁹ V. I. Ofitserov, Z. V. Pushkareva, V. S. Mokrushin, and K. V. Aglitskaya, *Khim. Geterotsikl. Soedin.* **9**, 1292 (1973); *Informationstienst*, **1**, 255 (1974).

⁸⁰ Ger. Offen. 2,204,201 [*CA* **77**, 140163 (1972)].

⁸¹ L. Henriksen and H. Autrup, *Acta Chem. Scand.* **26**, 3342 (1972).

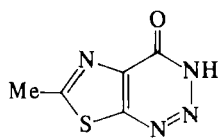
⁸² F. Fries, R. Walter, and K. Schilling, *Liebigs Ann. Chem.* **516**, 248 (1935).

⁸³ G. Ege and E. Beisiegel, *Angew. Chem., Int. Ed. Engl.* **7**, 303 (1968).

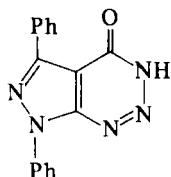
⁸⁴ J. R. Beck and J. A. Yahner, *J. Org. Chem.* **38**, 2450 (1973).

⁸⁵ F. Sauter and W. Deinhammer, *Monatsh. Chem.* **104**, 1586 (1973).

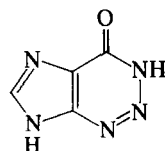
or a little piperidine.⁸⁶⁻⁹⁰ Initial attempts to extend this route to the analogous 1-alkyltriazenes (53, R = alkyl) were only moderately successful; it was claimed that the 1-alkyltriazenes were unstable, and that cyclization to the triazinones proceeded in low to moderate yield.⁹¹ It has subsequently been demonstrated, however, that much improved yields of the triazenes (53, R = alkyl) can be obtained under carefully controlled conditions.⁹² Le Blanc and Vaughan have carried out a thorough investigation of the reactions of diazotized anthranilic esters with a variety of primary aliphatic amines; they confirmed that 1-alkyltriazenes can be obtained in good to excellent yields, and showed



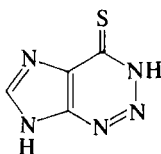
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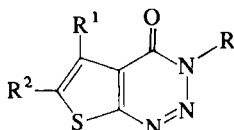
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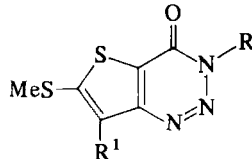
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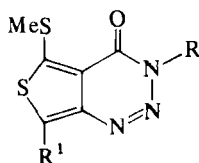
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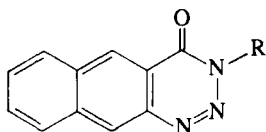
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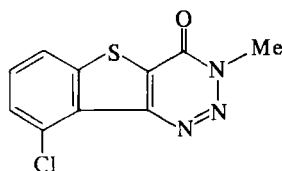
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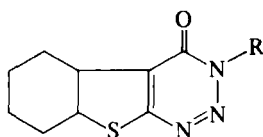
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⁸⁶ H. Mehner, *J. Prakt. Chem.* **63**, 241 (1901).

⁸⁷ F. D. Chattaway and A. J. Walker, *J. Chem. Soc.*, 323 (1927).

⁸⁸ P. Grammaticakis, *C.R. Acad. Sci. Ser. C* **243**, 2094 (1956).

⁸⁹ P. Grammaticakis, *Bull. Soc. Chim. Fr.*, 480 (1959).

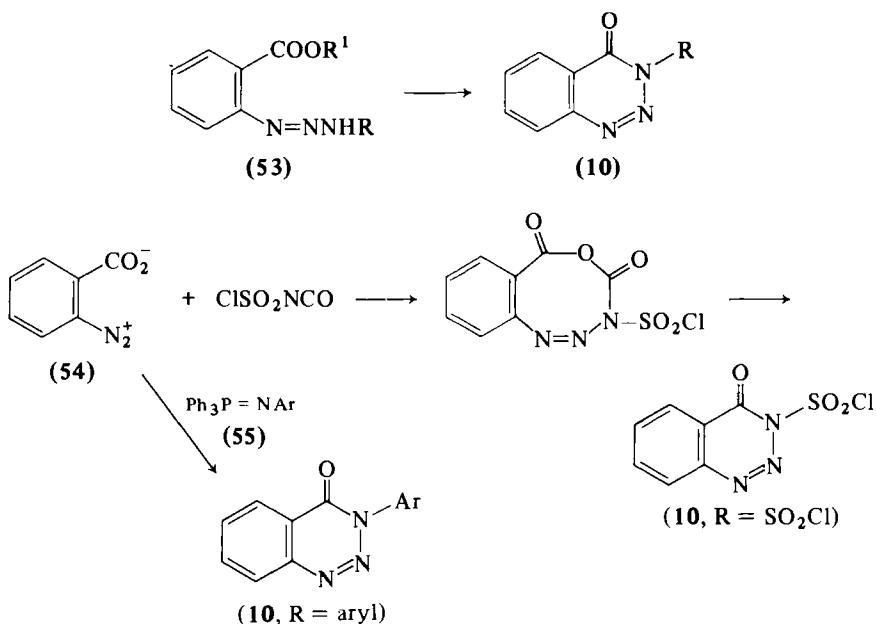
⁹⁰ H. N. E. Stevens and M. F. G. Stevens, *J. Chem. Soc. C*, 765 (1970).

⁹¹ E. M. van Heyningen, *J. Amer. Chem. Soc.* **77**, 6562 (1955).

⁹² W. F. Gilmore and R. N. Clark, *J. Heterocycl. Chem.* **6**, 809 (1969).

that these could be cyclized to 3-alkyl-1,2,3-benzotriazin-4(3*H*)-ones (**10**, R = alkyl) in excellent yields.⁹³

Reaction of the benzyne precursor (**54**) with triphenylphosphine arylimides (**55**) has been shown to give 3-aryl-1,2,3-benzotriazin-4(3*H*)-ones in poor (< 20%) yield and, while of mechanistic interest, these reactions are of no synthetic significance.⁹⁴ Another surprising reaction was reported recently by Moriconi and Shimakawa,⁹⁵ who found that



treatment of **54** with chlorosulfonyl isocyanate gave the chlorosulfonyl-triazinone (**10**, R = SO_2Cl) in 80% yield. The chlorosulfonyl derivative, although a crystalline solid, was unstable, and attempts to recrystallize it from methanol resulted in conversion into 1,2,3-benzotriazin-4(3*H*)-one in high yield. Reaction of **54** with *N,N*-bis(chlorosulfonyl)urea also gave ultimately **10**, R = H in 20% yield.

5. Condensed 4-Amino- and 4-Imino-1,2,3-triazines

Condensed 4-amino- and 4-imino-1,2,3-triazines can be prepared by two general cyclization processes which are directly analogous to the methods used for the preparation of condensed 1,2,3-triazin-4(3*H*)-ones, namely (i) diazotization of an *o*-aminobenzamidine, and (ii) cyclization

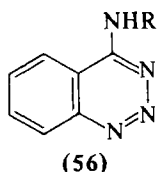
⁹³ R. J. Le Blanc and K. Vaughan, *Can. J. Chem.* **50**, 2544 (1972).

⁹⁴ T. Kawashima and N. Inamoto, *Bull. Chem. Soc. Jap.* **45**, 3504 (1972).

⁹⁵ E. J. Moriconi and Y. Shimakawa, *J. Org. Chem.* **37**, 196 (1972).

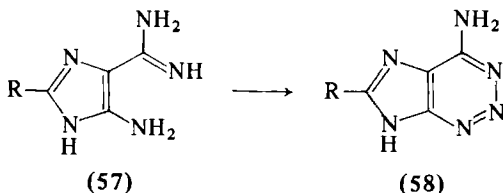
of a 1-aryl-3-(*o*-cyanophenyl)triazene. Treatment of 1,2,3-benzotriazine-4(3*H*)-thione or, better, 4-methylthio-1,2,3-benzotriazine with amines also constitutes a useful and much used procedure for preparation of the corresponding 4-amino derivatives.

For many years it was believed that anthranilonitrile did not react with either ammonia or hydrazine to give the corresponding amidines,^{45,96} and consequently, 4-amino- (**56**, R = H) and 4-hydrazino-1,2,3-benzotriazine (**56**, R = NH₂) were first prepared by reaction of 4-methylthio-1,2,3-benzotriazine with ammonia and hydrazine, respectively.⁴⁵ In general, alkylamines react readily with 1,2,3-benzotriazine-4(3*H*)-thione (**39**, R = H) to give the corresponding 4-amino derivatives



(**56**),⁹⁷ but arylamines normally are not sufficiently nucleophilic to react, and preparation of the 4-arylamino derivatives necessitates the use of 4-methylthio-1,2,3-benzotriazine.⁷⁷

Parnell has reexamined the reaction of anthranilonitrile with ammonia, found that *o*-aminobenzamidine can in fact be prepared relatively easily, and shown that it is converted into **56**, R = H, on diazotization.⁴¹ Reaction of **57** under the same conditions gives **58**.⁹⁸ Treatment of *N,N'*-diaryl-*o*-aminobenzamidines (**59**) with nitrous acid



gives the 3-aryl-4-arylimino-3,4-dihydro-1,2,3-benzotriazines (**60**),^{99,100} and the related condensed systems **61**–**65** have been prepared similarly from 2-(*o*-aminophenyl)-imidazole,¹⁰¹ -benzimidazole,¹⁰² and per-

⁹⁶ A. Pinner, "Die Iminoäther," p. 192, Berlin, 1892.

⁹⁷ E. E. Gilbert and B. Veldhuis, *J. Heterocycl. Chem.* **6**, 779 (1969).

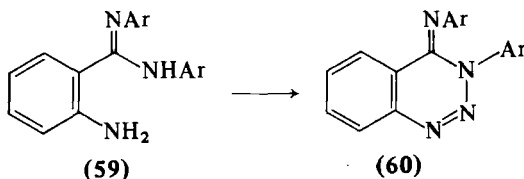
⁹⁸ D. W. Woolley and E. Shaw, *J. Biol. Chem.* **194**, 641 (1952).

⁹⁹ R. C. Shah, *J. Indian Inst. Sci.* **7**, 205 (1924) [*CA* **19**, 645 (1925)].

¹⁰⁰ M. W. Partridge and M. F. G. Stevens, *J. Chem. Soc.*, 3663 (1964).

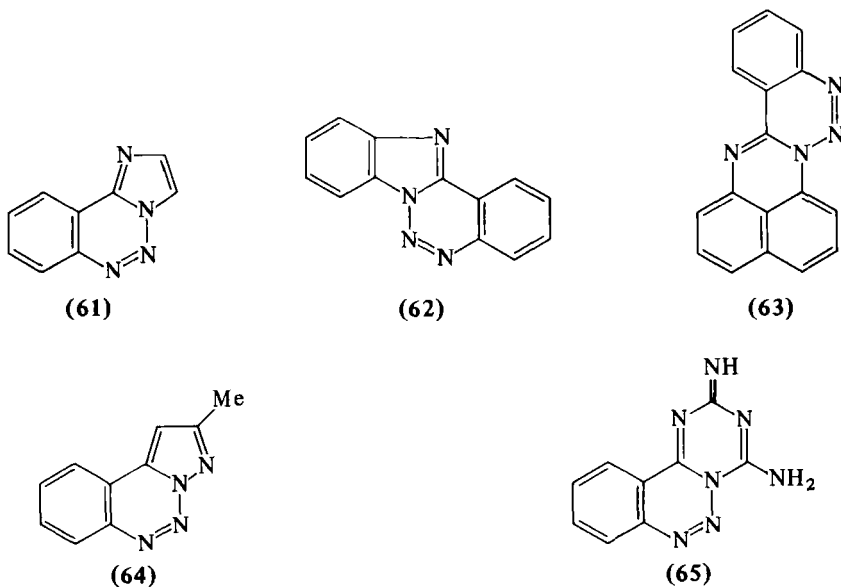
¹⁰¹ I. E. Balaban and H. King, *J. Chem. Soc.*, 2701 (1925).

¹⁰² S. von Niementowski, *Chem. Ber.* **31**, 314 (1898).



imidine,¹⁰³ 5-(*o*-aminophenyl)-3-methylpyrazole,¹⁰⁴ and 2-(*o*-aminophenyl)-4,6-diamino-1,3,5-triazine,¹⁰⁵ respectively. A number of substituted analogs of 62 have also been prepared in this way.¹⁰⁶

Cyclization of 1-aryl-3-(*o*-cyanophenyl)triazenes (66) to the 3-aryl-4-imino-3,4-dihydro-1,2,3-benzotriazines (67) has been studied in some detail by Stevens and Stevens.⁹⁰ Compounds in which the aryl substituent R is an electron-donating or mildly electron-withdrawing group (H, *o*-Me, *o*-Cl) undergo smooth ring closure to 67 when heated in either 70% aqueous ethanol or in 95% ethanol containing 2% piperidine. Compounds in which R is a powerfully electron-withdrawing group (*o*-NO₂, *p*-NO₂, *o*-CN, *p*-CN), on the other hand, undergo both ring closure and Dimroth rearrangement to give the 4-arylamino-1,2,3-benzotriazines (68), while the *m*-nitro and *m*-cyano derivatives show

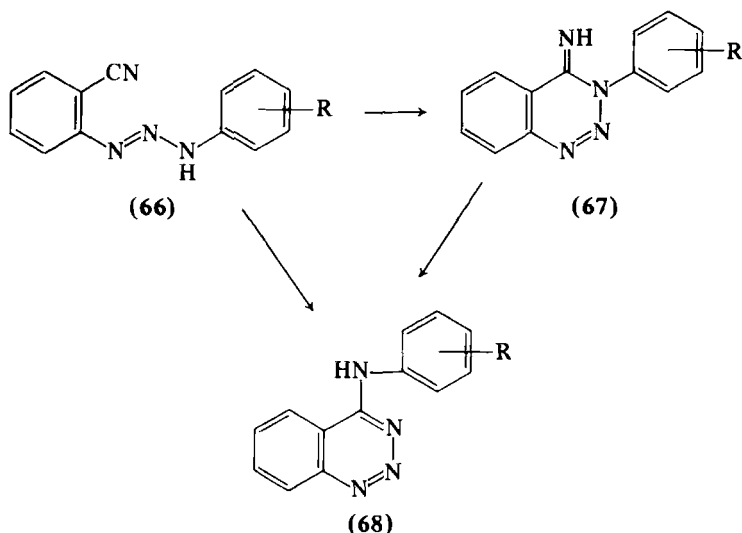


¹⁰³ F. Sachs and M. Steiner, *Chem. Ber.* **42**, 3674 (1909).

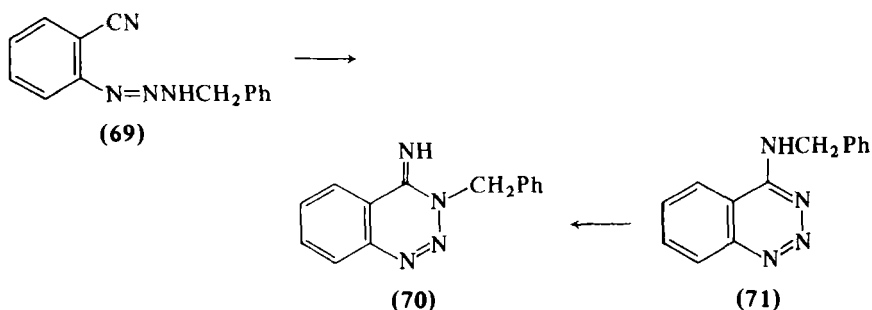
¹⁰⁴ E. Koenigs and J. Freund, *Chem. Ber.* **80**, 143 (1947).

¹⁰⁵ S. M. Mackenzie and M. F. G. Stevens, *J. Chem. Soc. C*, 2298 (1970).

¹⁰⁶ L. L. Zaika and M. M. Joullié, *J. Heterocycl. Chem.* **3**, 289 (1966).

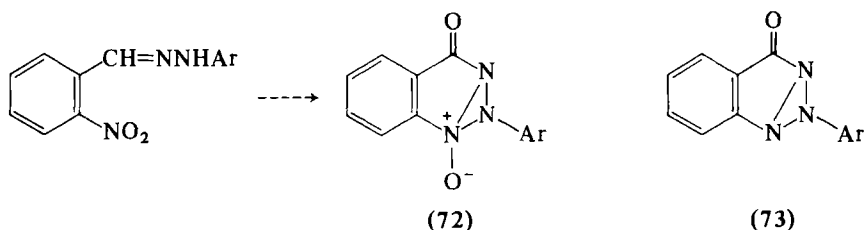


intermediate behavior inasmuch as the imino intermediates (67, R = *m*-NO₂, *m*-CN) can be isolated and subsequently isomerized to 68, R = *m*-NO₂, *m*-CN. The iminotriazines (67, R = H, *o*-Me, *o*-Cl) also rearrange to the arylamino isomers (68, R = H, *o*-Me, *o*-Cl) when heated in either 95% ethanol or 2 *N* hydrochloric acid. These results are fully consistent with known substituent effects in other Dimroth rearrangements, but the results obtained by Stevens and Stevens with 1-arylalkyl-3(*o*-cyanophenyl)triazines are less readily explained. Cyclization of 1-benzyl-3-(*o*-cyanophenyl)triazene (69), for example, gives 70, which does not rearrange when heated in either 70% aqueous ethanol or 2 *N* hydrochloric acid. On the contrary, 4-benzylamino-1,2,3-benzotriazine (71), prepared from 4-methylthio-1,2,3-benzotriazine and benzylamine, undergoes the reverse rearrangement to give 70.



B. TRIAZINIUM BETAINES

Mild oxidation of *o*-nitrobenzaldehyde arylhydrazones with either bromine and sodium acetate or lead tetraacetate results in the overall loss of two hydrogen atoms and production of a class of *N*-aryl heterocycles, the structure of which was the subject of uncertainty and some controversy for more than fifty years. These oxidation products were first prepared and investigated by Chattaway,¹⁰⁷⁻¹¹⁴ who described them as "isodiazomethanes" and formulated them as the triaziridine derivatives **72**. Structural assignment was based entirely on evidence from degradation studies; in particular, Chattaway showed that reduction of



"**72**" with stannous chloride resulted in the loss of a single oxygen atom and formation of a second class of compound which he represented as **73**.

In a reinvestigation of this work, Gibson,¹¹⁵ partly on the basis of mechanistic reasoning and partly as a result of spectroscopic (UV, IR) studies, suggested that the initial oxidation products were better represented as the isomeric arylazoanthranil *N*-oxides (**74**), and the stannous chloride reduction products as the dipolar species **75**. These



¹⁰⁷ F. D. Chattaway and A. J. Walker, *J. Chem. Soc.*, 2407 (1925).

¹⁰⁸ F. D. Chattaway and A. J. Walker, *J. Chem. Soc.*, 232 (1927).

¹⁰⁹ F. D. Chattaway and A. B. Adamson, *J. Chem. Soc.*, 157 (1930).

¹¹⁰ F. D. Chattaway and A. B. Adamson, *J. Chem. Soc.*, 2787, 2792 (1931).

¹¹¹ F. D. Chattaway and G. D. Parkes, *J. Chem. Soc.*, 1005 (1935).

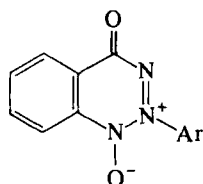
¹¹² F. D. Chattaway and A. B. Adamson, *J. Chem. Soc.*, 843 (1930).

¹¹³ G. D. Parkes and E. d'A. Burney, *J. Chem. Soc.*, 1619 (1935).

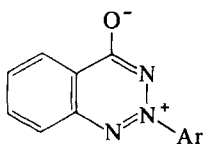
¹¹⁴ See pp. 27-30 in Erickson.¹

¹¹⁵ M. S. Gibson, *Tetrahedron* **18**, 1377 (1962); *Nature (London)* **193**, 474 (1962).

assignments were subsequently challenged by Kerber,¹¹⁶ who pointed out that Gibson's spectroscopic data were probably not consistent with structure **75**, and that structure **74** was improbable inasmuch that anthranil N-oxides are a rare, if not unknown, class of heterocycle. Kerber then proposed the triazininium betaine structures **76** and **77** for the oxidation and reduction products, respectively, and his assignments, like those of Gibson, were based partly on mechanistic reasoning and partly on spectroscopic (IR, UV, NMR, MS) evidence. The structures **76** and **77** proposed by Kerber have now been unambiguously confirmed by McKillop and Kobylecki,^{117,118} who developed a novel method for the

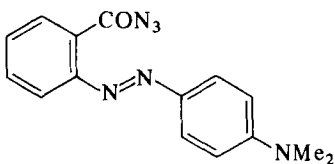


(76)



(77)

preparation of **77** (Ar = Ph, *p*-MeC₆H₄, *p*-BrC₆H₄; for details see p. 251). The same workers also carried out detailed spectroscopic studies on the two series of betaines **76** and **77** and showed that useful structural correlations could be drawn from the UV and mass spectra. Within this context it is interesting to note the unusual situation that exists with respect to the betaine **77**, Ar = *p*-Me₂NC₆H₄. Jennen claimed in 1956 that reaction of anthranilamide with *p*-*N,N*-dimethylaminonitrosobenzene gave **77**, Ar = *p*-Me₂NC₆H₄,¹¹⁹ but Kerber later showed this conclusion to be incorrect and established that the product of reaction



(78)

was in fact 4,4'-*bis-N,N*-dimethylaminoazoxybenzene.¹¹⁶ Thermolysis of the azide **78** was also reported to result in formation of **77**, Ar = *p*-Me₂NC₆H₄, but this claim is now regarded as doubtful in view of the

¹¹⁶ R. C. Kerber, *J. Org. Chem.* **37**, 1587 (1972).

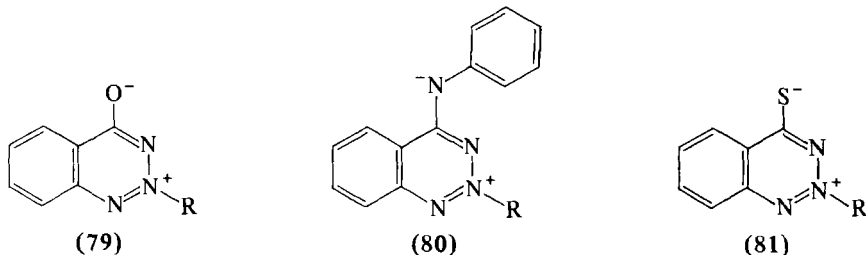
¹¹⁷ A. McKillop and R. J. Kobylecki, *J. Org. Chem.* **39**, 2710 (1974).

¹¹⁸ R. J. Kobylecki, Ph.D. Thesis, University of East Anglia, 1973.

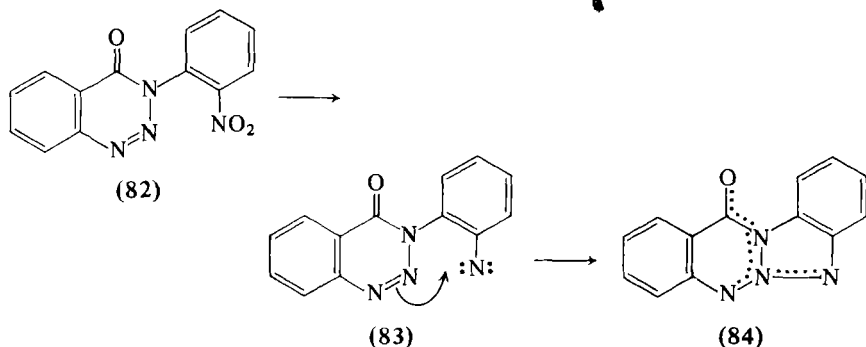
¹¹⁹ J. J. Jennen, *Meded. Vlaam. Chem. Ver.* **18**, 43 (1956) [*CA* **51**, 5094 (1957)].

known spectroscopic properties of compounds of the general type **77**.^{120,121}

Two classes of betaines related to **77**, namely **79**, R = alkyl, and **80**, R = alkyl, have been prepared independently by alkylation of **10**, R = H,^{122,123} and of **56**, R = Ph,^{124,125} respectively (for details see p. 247), while the thioxotriazinium betaines (**81**, R = alkyl) have been obtained



by treatment of **79**, R = alkyl, with phosphorus pentasulfide.¹²² The highly resonance-stabilized triazinium betaine **84** has been prepared by triethyl phosphite reduction of 3-(*o*-nitrophenyl)-1,2,3-benzotriazin-4(3*H*)-one (**82**).¹²⁶ The chemical and spectroscopic properties of **84**,



which was assumed to be formed via the intermediate nitrene (**83**), are fully consistent with the assigned structure. The related stabilized betaines **86** and **88** have been prepared similarly from the triazine **85** and the mesoionic triazine **87**, respectively.¹²⁷

¹²⁰ R. C. Kerber and P. J. Heffron, *J. Org. Chem.* **37**, 1592 (1972).

¹²¹ R. C. Kerber, personal communication.

¹²² G. Wagner and H. Gentzsch, *Pharmazie* **11**, 629 (1968).

¹²³ G. Wagner and H. Gentzsch, *Arch. Pharm. (Weinheim)* **301**, 923 (1968) [*CA* **70**, 106825 (1969)].

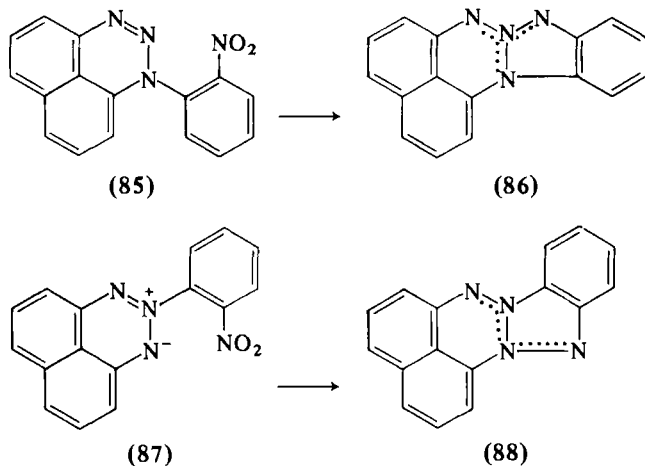
¹²⁴ H. N. E. Stevens and M. F. G. Stevens, *J. Chem. Soc. C*, 2284 (1970).

¹²⁵ H. N. E. Stevens and M. F. G. Stevens, *J. Chem. Soc. C*, 2289 (1970).

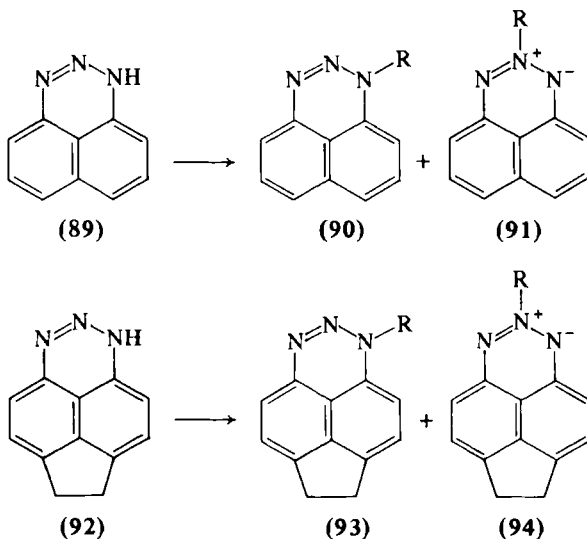
¹²⁶ A. W. Murray and K. Vaughan, *Chem. Commun.*, 1282 (1967).

¹²⁷ H. Sieper and P. Tavs, *Liebigs Ann. Chem.* **704**, 161 (1967).

Alkylation (with dialkyl sulfates, alkyl tosylates, and alkyl halides) and arylation (with nitro-activated aryl halides) of the 1*H*-naphtho[1,8-*de*]triazine (89) and of the structurally related 6,7-dihydro-1*H*-

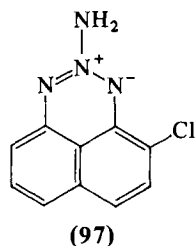
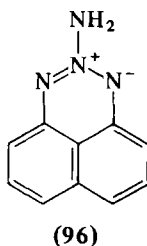
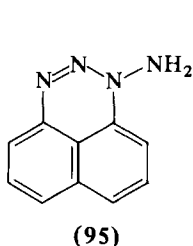


acenaphtho[5,6-*de*]triazine (92) has been shown to result in production of a mixture of the 1-alkylated or arylated derivatives 90 and 93 and the 2-alkylated and arylated derivatives 91 and 94, respectively (for details see p. 250).¹²⁸ Amination of 1*H*-naphtho[1,8-*de*]triazine (89) has been



¹²⁸ P. Tavs, H. Sieper, and H. Beecken, *Liebigs Ann. Chem.* 704, 150 (1967).

studied in some detail, as subsequent oxidation of the expected product of amination, the 1-amino derivative (95), constitutes a useful procedure for the preparation of the interesting and highly reactive "meta" aryne, 1,8-dehydronaphthalene.¹²⁹⁻¹³¹ Treatment of 89 with hydroxylamine *O*-sulfonic acid results in formation of a mixture of the 1-amino derivative



(95) and 1-amino-8-azidonaphthalene.¹³² When chloramine is used as the reagent, however, a mixture of 95 and the 2-amino derivative 96 is obtained, together with a small amount of 2-amino-4-chloronaphtho[1,8-*de*]triazine (97). The betaine 96 is believed to undergo chlorination to produce 97, and has also been shown to serve as the precursor for 1-amino-8-azidonaphthalene, into which it is converted by base cleavage of the heterocyclic ring.

C. REACTIONS

1. Hydrolysis

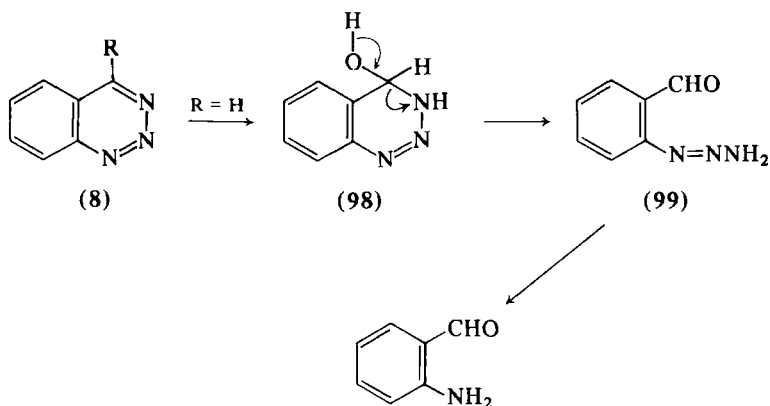
Hydrolysis of condensed 1,2,3-triazines results in cleavage of the heterocyclic ring and is in many respects an unexceptional and fully predictable type of reaction. The relative ease with which ring fission takes place, and the products formed, depend almost entirely on the nature of the substituents at the 3- and 4-positions and on the reaction conditions employed. Moreover, hydrolysis under basic conditions normally leads to fission of the N_3-C_4 bond whereas under acidic conditions most 1,2,3-benzotriazine derivatives behave as "masked" diazonium compounds, and hydrolysis proceeds with fission of the N_2-N_3 bond and transient formation of a diazonium compound, from which the observed products are ultimately derived. Hydrolysis of certain derivatives probably also involves covalent hydration as the key step.

¹²⁹ C. W. Rees and R. C. Storr, *J. Chem. Soc. C*, 760 (1969).

¹³⁰ C. W. Rees and R. C. Storr, *J. Chem. Soc. C*, 765 (1969).

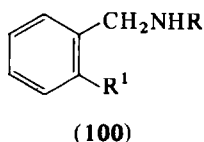
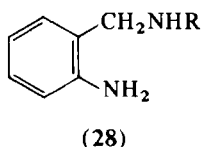
¹³¹ R. W. Hoffmann, G. Guhn, M. Preiss, and B. Dittrich, *J. Chem. Soc. C*, 769 (1969).

¹³² C. W. Rees and R. C. Storr, *J. Chem. Soc. C*, 756 (1969).

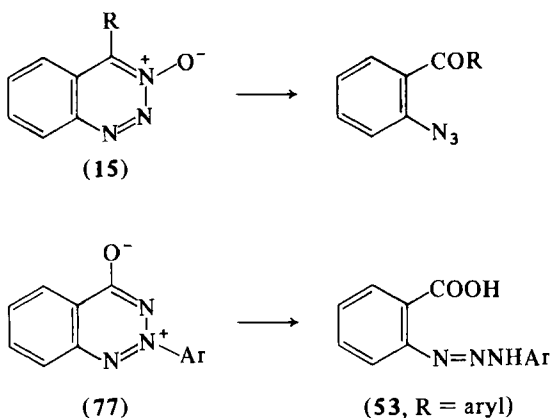


1,2,3-Benzotriazine (**8**, $R = H$), for example, can be isolated as a reasonably stable, colorless crystalline solid, but it reacts rapidly in solution with water to give *o*-aminobenzaldehyde, presumably by initial covalent hydration to give **98**, which decomposes to *o*-aminobenzaldehyde via the triazene **99**.²⁹ Reaction of **8**, $R = H$, with other nucleophiles also occurs readily, while 4-substituted 1,2,3-benzotriazines react similarly but more slowly, as expected, owing to a combination of steric and electronic effects.

Hydrolytic cleavage of condensed 1,2,3-triazine derivatives is normally a straightforward, high-yield process which results in production of one or other of several distinct types of product. 3-Alkyl- and 3-aryl-3,4-dihydro-1,2,3-benzotriazines, for example, undergo facile hydrolysis in concentrated hydrochloric acid to give, via the diazonium compound, *N*-alkyl- and *N*-aryl-substituted *o*-chlorobenzylamines (**100**, $R^1 = Cl$).⁵¹ If the reaction is carried out in water or in dilute mineral acid, the corresponding *N*-alkyl and *N*-aryl-substituted *o*-hydroxybenzylamines (**100**, $R^1 = OH$) are obtained.



Treatment of condensed 1,2,3-triazine 3-oxides (**15**) with either acid or base results in formation of *o*-azido carbonyl compounds.^{35-38,46} Alkaline hydrolysis of the betaines **77**, on the other hand, gives the triazenes **53**, $R = \text{aryl}$, possibly via rearrangement of the aryl group from N_2 to N_3 to give **10**, $R = \text{aryl}$, followed by ring cleavage.⁸⁷ The



analogous 2-alkyl betaines do not apparently react similarly, as treatment of **79**, R = Me, with dilute sodium hydroxide is reported to result in demethylation.¹²²

Hydrolysis of 3-alkyl-1,2,3-benzotriazin-4(3*H*)-ones (**10**, R = alkyl) with cold, aqueous potassium hydroxide leads to anthranilic acid derivatives.⁶⁵ The related 3-aryl-1,2,3-benzotriazin-4(3*H*)-ones (**10**, R = aryl) react less readily, but on treatment with hot aqueous or alcoholic potassium hydroxide are converted into 3-aryltriazenes (**53**, R = aryl) which, on further reaction, give anthranilic acids.⁸⁶

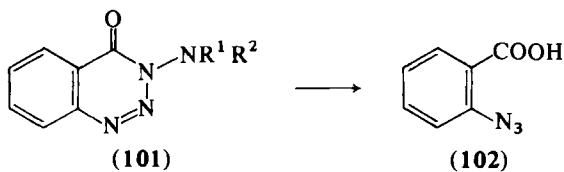
Hot, dilute sulfuric acid hydrolysis of **10**, R = alkyl, aryl initially gives anthranilic acid, which is converted into salicylic acid on prolonged reaction.⁶⁸ When dilute hydrochloric acid is employed with the same substrates *N*-alkyl- and *N*-arylsalicylamides are formed,¹³³ but concentrated hydrochloric acid results in the formation of *o*-chlorobenzoic acid.^{65,68,71,86}

The reactions of 3-amino-1,2,3-benzotriazin-4(3*H*)-one and a number of its derivatives (**101a–g**) under both acidic and basic media have been investigated in some detail by Gibson and Green.¹³⁴ Earlier work by Heller and his colleagues had apparently established that treatment of **101a–e** with hot aqueous sodium hydroxide solution gave *o*-azido-benzoic acid (**102**), and Gibson and Green showed that **101f** behaved similarly. The benzyldienamino derivative **101g**, however, was reported by Heller to yield benzaldehyde *o*-carboxyphenylhydrazone (**103**) under basic conditions, and benzimidazolone (**104**) under acidic conditions.

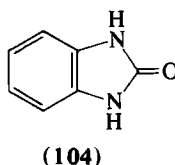
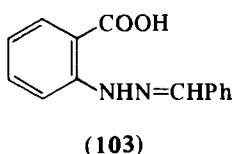
The seemingly anomalous behavior of **101g** has now been resolved. Gibson and Green first of all showed that hydrolysis of **101a** gives in

¹³³ H. Meyer, *Liebigs Ann. Chem.* **351**, 267 (1907).

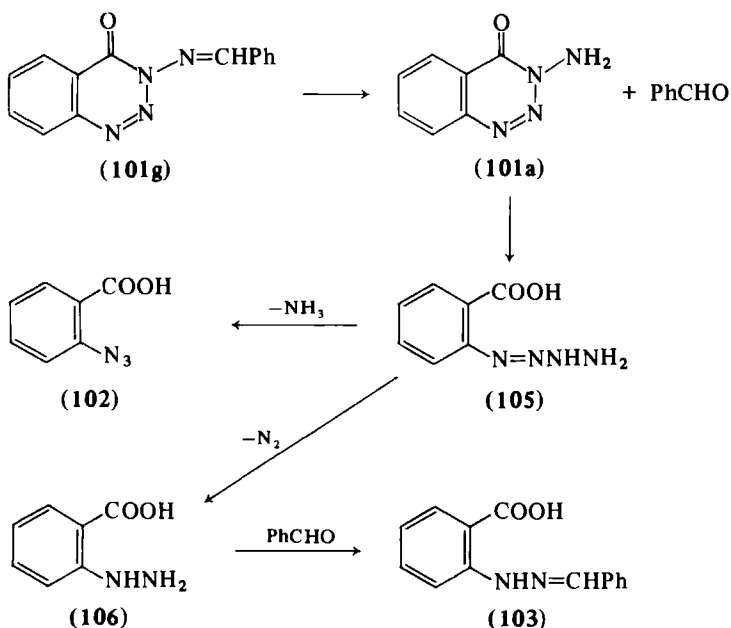
¹³⁴ M. S. Gibson and M. Green, *Tetrahedron* **21**, 2191 (1965).



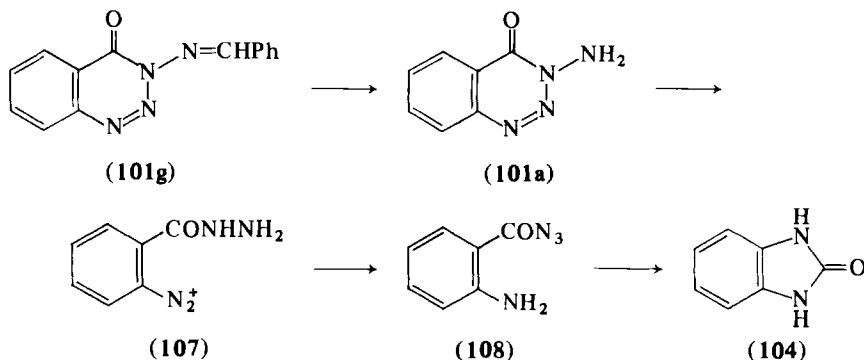
- a**, $R^1 = R^2 = H$
b, $R^1 = H, R^2 = Ac$
c, $R^1 = H, R^2 = CPh$
d, $R^1 = H, R^2 = COOMe$
e, $R^1 = H, R^2 = COOEt$
f, $R^1 = Me, R^2 = Ph$
g, $R^1, R^2 = CHPh$



fact a mixture of **102** and the hydrazine **106**; the presence of the latter compound was demonstrated by addition of benzaldehyde to the alkaline hydrolyzate from **101a** and isolation of the hydrazone **103**.



Reaction of **101g** under basic conditions was then shown to result in initial cleavage of the imine to give benzaldehyde and **101a**, the latter of which then underwent further hydrolysis via the tetrazene **105** to give both **102** and **106**. Condensation of **106** with the benzaldehyde



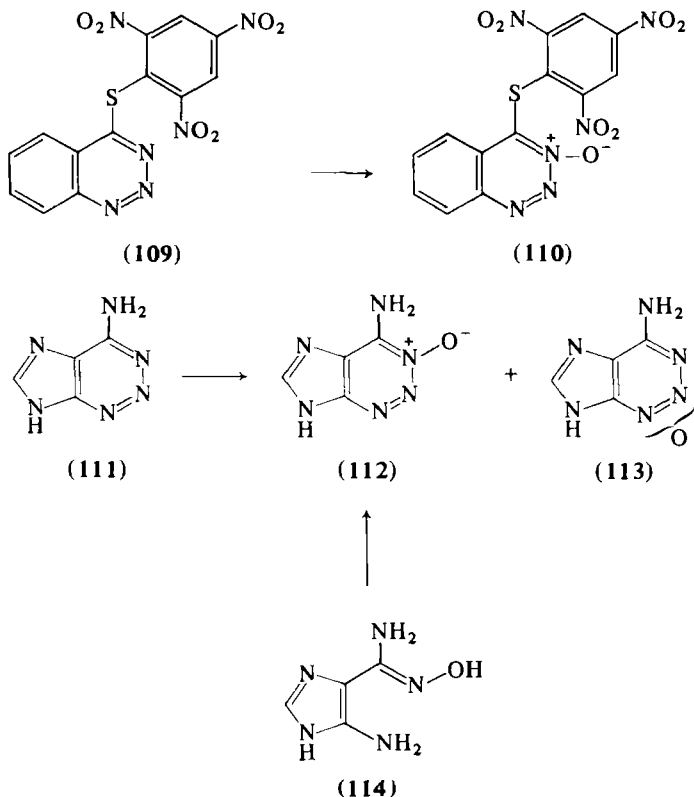
produced **103**. The hydrolysis pattern thus established for the benzyldeneamino derivative **101g** in base contrasts with that observed with the related *N*-acyl and *N*-carbalkoxy derivatives (**101b–e**), which have been shown conclusively to undergo initial nucleophilic attack at the endocyclic, *not* the exocyclic, carbonyl group.

Hydrolysis of **101g** in acidic medium is also a somewhat complicated process, and the reaction course depends both on the strength of the acid used and on the reaction temperature. With hot hydrochloric acid, initial hydrolysis of the imine gives benzaldehyde and **101a**, which undergoes ring opening by cleavage of the N_2-N_3 bond. Trans-diazotization of the resultant diazonium intermediate (**107**) gives anthranilazide (**108**), Curtius rearrangement of which leads to benzimidazolone (**104**).

2. Oxidation and Reduction

Very little is known about the susceptibility of the ring nitrogen atoms in 1,2,3-triazine derivatives to N-oxidation. Attempts to oxidize the *N*-aryl- **77** and *N*-alkyltriazinium (**79**) betaines to the corresponding 1-oxides under a variety of conditions were unsuccessful, and the betaines were recovered unchanged even after prolonged exposure to powerful oxidants.^{117,118} It has been reported that oxidation of the 4-arylthio-1,2,3-benzotriazine (**109**) takes place at nitrogen rather than sulfur, and the product has been formulated as the N_3 -oxide (**110**) or the N_1 -isomer.¹³⁵ The evidence in favor of structure **110**—the lack of bands

¹³⁵ B. Stanovnik and M. Tisler, *J. Heterocycl. Chem.* **8**, 785 (1971).



characteristic of the sulfoxide group in the IR spectrum, and the observation of an intense peak in the mass spectrum due to loss of the 2,4,6-trinitrophenylthio residue—is, however, not completely unambiguous. Oxidation of the aminotriazine 111, on the other hand, gives a mixture of the N-oxides 112 and 113 in the ratio of 3 : 1. The structure of 112 was confirmed by independent synthesis from 114.¹³⁶

In contrast to the above situation with respect to oxidation of the ring nitrogen atoms of 1,2,3-triazines, oxidation of derivatives of 3-amino-1,2,3-benzotriazin-4(3H)-one (101a) has proved to be of considerable interest and has been investigated in some detail by Rees and his colleagues.^{137,138} Treatment of 101a with lead tetraacetate at 80° has been shown to give benzyne in very low yield,¹³⁹ but at room

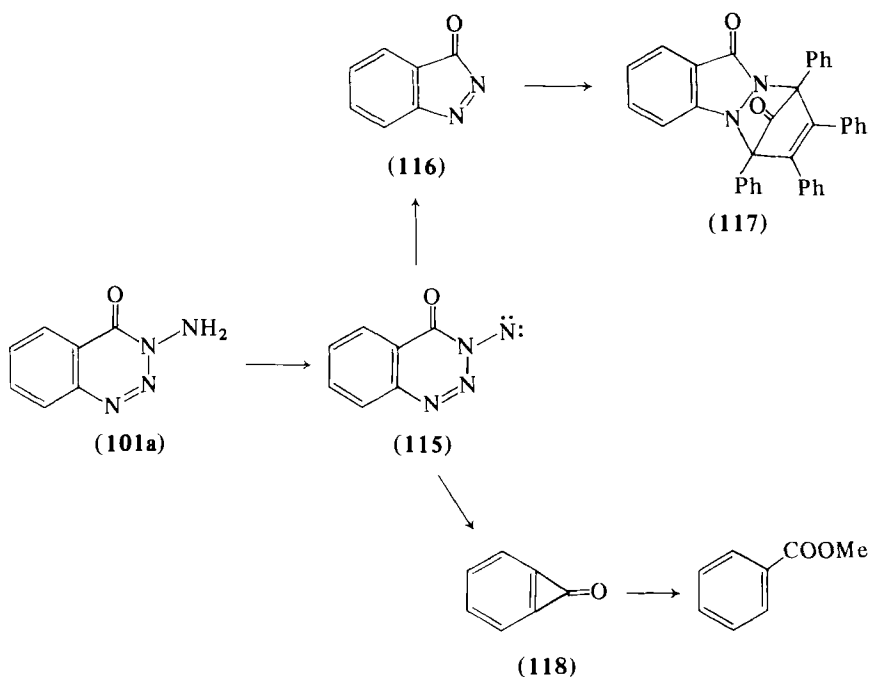
¹³⁶ M. A. Stevens, H. W. Smith, and G. B. Brown, *J. Amer. Chem. Soc.* **82**, 3189 (1960).

¹³⁷ C. D. Campbell and C. W. Rees, *J. Chem. Soc. C*, 742 (1969).

¹³⁸ J. Adamson, D. L. Forster, T. L. Gilchrist, and C. W. Rees, *Chem. Commun.*, 221 (1969).

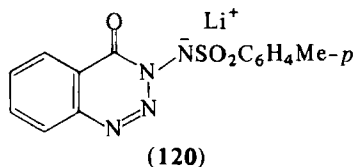
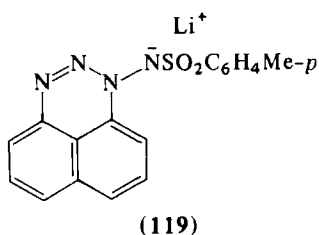
¹³⁹ C. D. Campbell, Ph.D. Thesis, University of London, 1966.

temperatures this reaction pathway is virtually nonoperative.¹³⁷ Instead, two independent courses of reaction have been established, both of which have been postulated to proceed via the intermediacy of the nitrene **115**.³⁹ Oxidation of **101a** with lead tetraacetate in dichloromethane results in the loss of one molecule of nitrogen from **115** and formation of the unstable indazolone **116**; this latter species can



readily be trapped as the adduct **117** when the reaction is carried out in the presence of tetracyclone. When methanol is used as solvent, on the other hand, **115** decomposes to benzocyclopropenone (**118**) with the loss of two molecules of nitrogen; **118** is, of course, a highly reactive intermediate and is converted into methyl benzoate under the reaction conditions. Formation of **118** is consistent with the results obtained from the oxidation of a number of 6- and 7-substituted derivatives of **101a**; treatment of the 6-chloro derivative with lead tetraacetate in methanol, for example, gives a mixture of methyl *m*-chlorobenzoate (58.5%) and methyl *p*-chlorobenzoate (11.5%). Moreover, Hückel calculations indicate that concerted loss of two molecules of nitrogen from **115** to give **118** is energetically reasonable, while the results from ¹⁵N labeling studies are similarly in accord with a concerted mechanism for the loss of nitrogen from **115** and formation of indazolone (**116**).³⁹

Oxidation of 1-aminonaphtho[1,8-*de*]triazine (95) with lead tetraacetate has been shown by trapping experiments to result in formation of 1,8-dehydronaphthalene, again almost certainly via initial formation of the nitrene followed by loss of two molecules of nitrogen.¹²⁹⁻¹³¹ The same "meta" aryne is formed during the thermolysis of the lithium salt of 1-*p*-toluenesulfonylaminonaphtho[1,8-*de*]triazine (119), in a formal oxidation process,¹³¹ while benzocyclopropenone (118) has similarly been generated by photolysis of the lithium salt 120.¹⁴⁰



The —N=N=N— functional group is normally unstable to reducing conditions, both in 1,3-disubstituted triazenes¹⁴¹ and in condensed 1,2,3-triazines. A wide range of reducing agents has been employed for the hydrogenolysis of many 1,2,3-benzotriazine derivatives, and, as with hydrolysis, reductive cleavage under certain conditions can best be rationalized on the basis that the heterocyclic system is functioning as a "masked" diazonium compound. Thus, 3-aryl-1,2,3-benzotriazin-4(3*H*)-ones (10, R = aryl) are apparently inert to the action of sodium amalgam,⁸⁷ but are converted into anthranilic acids on treatment with stannous chloride⁸⁶ and into substituted benzanilides on reduction with aqueous titanous chloride.¹³³ Reductive cleavage of 10, R = alkyl, aryl, with Raney nickel/hydrazine mixtures gives anthranilamides in good yield.¹⁴² In certain cases it is possible to reduce a functional group located in the nonheterocyclic portion of the molecule without at the same time destroying the triazinone ring; catalytic reduction of 3-(*o*-nitrophenyl)-1,2,3-benzotriazin-4(3*H*)-one (82), for example, gives the corresponding 3-*o*-aminophenyl derivative.¹⁴² In other cases, the 3-substituent may be hydrogenolyzed; reduction of 3-amino-1,2,3-benzotriazin-4(3*H*)-one (101a) with zinc and acetic acid, for example, gives 1,2,3-benzotriazin-4-one (10, R = H).¹⁴³ The relatively unstable 3-

¹⁴⁰ M. S. Ao, E. M. Burgess, A. Schauer, and E. A. Taylor, *Chem. Commun.*, 220 (1969).

¹⁴¹ P. A. S. Smith, "Open Chain Nitrogen Compounds." Benjamin, New York, 1966.

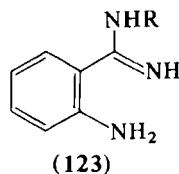
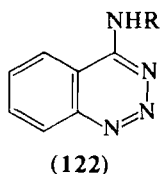
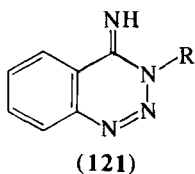
¹⁴² H. N. E. Stevens and M. F. G. Stevens, *J. Chem. Soc. C*, 2308 (1970).

¹⁴³ C. Thode, *J. Prakt. Chem.* 69, 92 (1904).

alkyl- and 3-aryl-3,4-dihydro-1,2,3-benzotriazines (29) are converted into substituted *o*-aminobenzylamines on treatment with sodium/ethanol.⁵¹

Reductive removal of the N₁-oxide oxygen atom of the triazinium betaines (76) can be readily accomplished either by heating the betaine N-oxides in ethanol, or, more efficiently, by treatment with stannous chloride. Further reduction of the resultant betaines (77) with tin/hydrochloric acid results in ring cleavage and formation of arylhydrazides or anthranilic acid.⁸⁷

One very interesting aspect of the chemistry of aminoindazoles and 1,2,3-benzotriazines is the ease with which either of the two ring systems can be converted into the other. As mentioned earlier (see p. 219) oxidation of 1-, 2-, and 3-aminoindazole gives 1,2,3-benzotriazine derivatives in good yield. Reduction of certain types of 1,2,3-benzotriazine derivatives, on the other hand, gives substituted indazoles. Treatment of 4-alkyl- and 4-aryl-1,2,3-benzotriazine 3-oxides (15) with zinc/acetic acid, for example, gives substituted indazoles.³⁸ Reduction of 10, R = H, with zinc/ammonium hydroxide is reported to give indazolone (116),⁴² while sodium/ethanol or sodium amalgam reduction of 4-amino-1,2,3-benzotriazine 3-oxide (20) gives 3-aminoindazole (9).^{41,43,44}



Reduction of the isomeric 1,2,3-benzotriazines 121 and 122 with Raney nickel/hydrazine has been studied in some detail.¹⁴² The 3-aryl-4-imino derivatives (121, R = Ph, *o*-ClC₆H₄) give low yields of *N*-phenylbenzamidine and *N*-*o*-chlorophenylbenzamidine, respectively, via reductive elimination of nitrogen; similar hydrogenolysis of the 1,2,3-triazine ring with loss of nitrogen has also been observed with the analogous benzimidazo[1,2-*c*][1,2,3]benzotriazine (62)¹⁴⁴ and the 1,3,5-triazino[1,2-*c*][1,2,3]benzotriazine (65)¹⁰⁵ systems. The arylalkyl derivative (121, R = CH₂Ph), on the other hand, gives a mixture of the benzamidine 123, R = CH₂Ph and 3-benzylaminoindazole together with a trace of 3-aminoindazole on treatment with Raney nickel/hydrazine,¹⁴² whereas reduction with stannous chloride in ethanol gives only 3-benzylaminoindazole.¹⁰⁰

The 4-aryl- and 4-arylalkylamino-1,2,3-benzotriazines (122) are considerably more resistant to Raney nickel/hydrazine than the imino

¹⁴⁴ R. H. Spector and M. M. Joullié, *J. Heterocycl. Chem.* 6, 605 (1969).

isomers (121). Reduction of 122, R = Ph, gives a mixture of the benzamidine (123, R = Ph) and unchanged starting material, 122, R = *o*-ClC₆H₄, is unaffected by the reagent, and only the nitro group in 122, R = *m*-O₂NC₆H₄, is reduced. The benzylamino derivative (122, R = CH₂Ph gives the benzamidine (123, R = CH₂Ph), but, rather interestingly, the phenylethyl analog (122, R = CH₂CH₂Ph) is recovered unchanged even after prolonged reaction times. In fact, the triazine (122, R = CH₂CH₂Ph) appears to be unusually stable to reduction, and it has also been shown to be unaffected by lithium aluminum hydride.⁹⁰

3. Acylation, Alkylation, and Arylation

1,2,3-Benzotriazin-4(3*H*)-one (10, R = H) is an acidic compound. It is freely soluble in aqueous alkali and in ammonium hydroxide and forms a variety of metal salts, most of which are perfectly stable. It has been stated that the 4-hydroxy tautomer is the more important contributor to the structure for reasons of aromaticity (sic!),¹⁴⁵ but this assertion is undoubtedly incorrect, as it is well known that most heterocyclic lactams normally exist preferentially in the amide form.¹⁴⁶ Unfortunately no detailed studies have been carried out on the tautomeric equilibria in condensed 1,2,3-triazin-4(3*H*)-ones, but there are a few results available which indicate that the amide form (10, R = H) is the major contributor. (The alternative amide tautomer, 1,2,3-benzotriazin-4(1*H*)-one has not been seriously considered to be an important contributor.) The UV spectra of 10, R = H, and 10, R = Me, are virtually identical,¹¹⁸ as are those of 10, R = H, and the corresponding thione (39, R = H).⁹⁷ Consequently, both 10, R = H, and 39, R = H, exist predominantly as the amide and thioamide, respectively (see p. 262 for X-ray crystallographic data). Similar results have been reported for both the thieno[3,2-*e*]triazines (48) and the thieno[3,4-*e*]triazines (49), where the UV spectra of the unsubstituted compounds (48, 49, R = H) are reported to be "very similar" to those of the N₃-methyl derivatives (48, 49, R = Me).⁸⁰

It has been reported that the UV spectra of 1,2,3-benzotriazin-4(3*H*)-one (10, R = H), the corresponding triazinethione (39, R = H) and the 4-alkylamino-1,2,3-benzotriazines (56) formed by treatment of 39, R = H, with alkylamines are "nearly identical," and this has been taken as evidence that the compounds 56 actually exist as the 3,4-dihydro-4-imino tautomers.⁹⁷ This claim has not, however, been substantiated, and, in the absence of more definitive evidence, structure 56 is almost certainly the more accurate representation for these compounds.

¹⁴⁵ See p. 17 in Erickson,¹ and p. 788 in Horowitz.²

¹⁴⁶ A. R. Katritzky and J. M. Lagowski, *Advan. Heterocycl. Chem.* 1, 311, 339 (1963); 2, 28 (1963).

Early acylation experiments with **10**, R = H, were interpreted on the basis that reaction had occurred solely at N₃,^{42,68} but these conclusions were later challenged, and it was claimed that acylation also occurred on oxygen.¹⁴⁵ Reinvestigation of these reactions has established that acylation does in fact occur solely at N₃, and the claim for O-acylation must be regarded as specious.¹⁴⁷ Reaction of **10**, R = H, with *p*-toluenesulfonyl chloride¹⁴⁸ and with trichloromethylsulfenyl chloride¹⁴⁹⁻¹⁵² has also been shown to give the 3-substituted derivatives (**10**, R = *p*-MeC₆H₄SO₂, SClCl₃), respectively.

Early work on the alkylation of metal salts of **10**, R = H, was also interpreted on the basis of exclusive N₃-substitution,^{42,65,67,68} but this is now known to be incorrect.¹¹⁸ Under reaction conditions that have been widely employed for the N-alkylation of many heterocyclic lactams, **10**, R = H, does undergo substitution predominantly at N₃, as can readily be seen by comparison of products with genuine samples of 3-substituted 1,2,3-benzotriazin-4(3*H*)-ones prepared unambiguously by diazotization of the appropriately substituted anthranilamides. The presence of isomeric products can also, however, be readily established by spectral and chromatographic techniques. Wagner and Gentzsch found that treatment of **10**, R = H, with either dimethyl or diethyl sulfate or the corresponding alkyl halides under mild conditions gave a mixture of products, namely, the N₃-substituted derivative as the major product, a very small amount of the 4-alkoxy compound, and a third isomer, the structure of which they were unable to assign unambiguously.^{122,123} They suggested that these latter compounds were the N₂-methyl and N₂-ethyl betaines (**79**, R = Me, Et); the structure of **79**, R = Me, has now been unambiguously established, Wagner and Gentzsch's results have been verified, and it has been found that **79**, R = Me, can be readily obtained in good (71%) yield simply by treatment of a solution of **10**, R = H, in sodium hydroxide with dimethyl sulfate.¹¹⁷ Treatment of salts of **10**, R = H, with 2,3,4,6-tetraacetyl-β-D-glucopyranosyl bromide also gives a mixture of the N₂- and N₃-alkylated derivatives.¹²³

The relative extent of alkylation of **10**, R = H, at N₂ and N₃ has been observed to vary substantially with the reaction conditions employed, and it now appears likely that the N₂-alkylated compound is the product of kinetic control. The betaines (**79**) are reasonably stable compounds and can readily be isolated; they do, however, undergo both dealkylation (with regeneration of **10**, R = H) and rearrangement to the 3-isomers on

¹⁴⁷ M. S. Gibson and A. W. Murray, *J. Org. Chem.* **27**, 4083 (1962).

¹⁴⁸ G. Ege, *Chem. Ber.* **101**, 3079 (1968).

¹⁴⁹ U. S. Patent, 2,935,445 [*CA* **54**, 17782 (1960)].

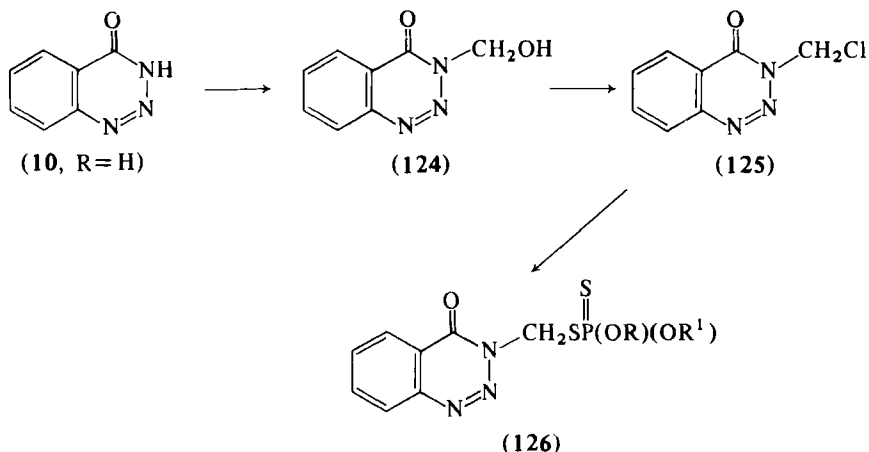
¹⁵⁰ C. Hennart, *Bull. Soc. Chim. Fr.*, 4691 (1967).

¹⁵¹ French Patent 1,489,235; *Chem. Abstr.* **69**, 43946 (1968).

¹⁵² Belgian Patent 696,711; *Chem. Abstr.* **71**, 101891 (1969).

exposure to strong base, and this isomerization can almost certainly also be effected both thermally and photolytically.¹¹⁸ Within this general context it is interesting that alkylation of **10**, R = H, with the very powerful and relatively unselective reagent triethyloxonium tetrafluoroborate has been reported to give exclusive N₃- and O-alkylation in the ratio 3 : 1.¹³⁵

Alkylation of **10**, R = H, with aqueous formaldehyde proceeds smoothly to give the 3-hydroxymethyl derivative (**124**).¹⁵³ This reaction is of considerable commercial importance, as subsequent reaction of **124** with thionyl chloride gives the corresponding chloromethyl derivative (**125**), from which the dithiophosphorus esters (**126**) can

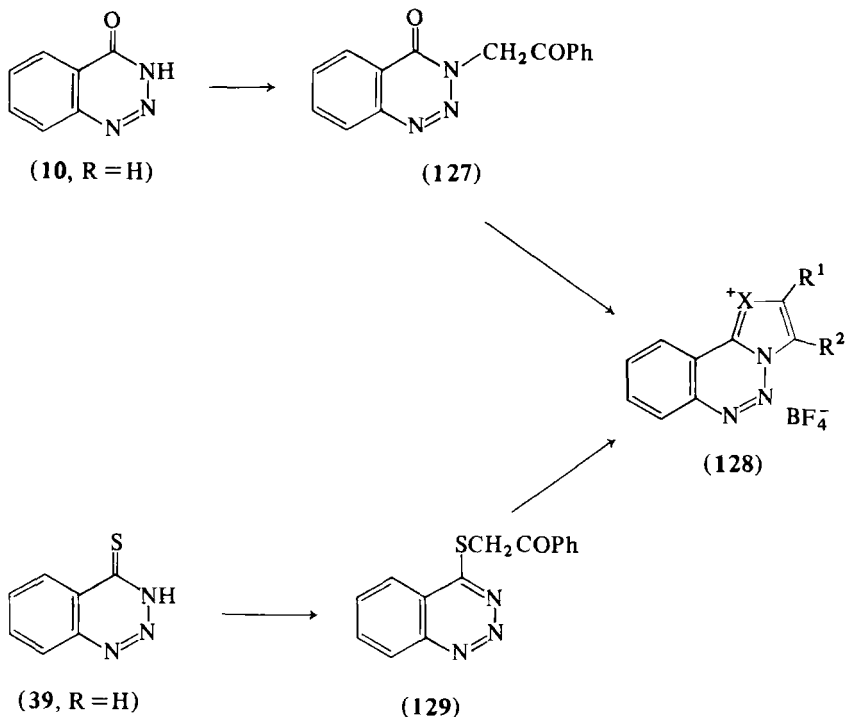


readily be obtained by treatment with ammonium salts of dithiophosphoric esters. Compounds of the type **126** have been found to exhibit powerful insecticidal properties and are discussed more fully later (see p. 269).

From the above discussion it is evident that alkylation of 1,2,3-benzotriazin-4-one results almost entirely in substitution at N₂ and/or N₃, and that alkylation on oxygen is at most a minor reaction. Alkylation of 1,2,3-benzotriazine-4(3*H*)-thione (**39**, R = H), on the other hand, leads to predominant or exclusive substitution on sulfur,^{43,74} presumably as a result of the greater nucleophilicity of sulfur compared to oxygen. This difference in reactivity between the oxygen (**10**, R = H) and sulfur (**39**, R = H) compounds has been elegantly demonstrated by Murray and Vaughan.¹⁵⁴ Treatment of the sodium salt of **10**, R = H, with phenacyl bromide gives the N₃-substituted derivative **127**, which, on

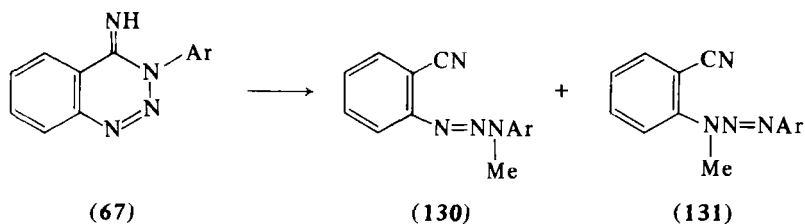
¹⁵³ See, e.g., M. Hafez, *Agr. Res. Rev.* **38**, 47 (1960) [*CA* **55**, 26351 (1961)] and others under "Uses."

¹⁵⁴ A. W. Murray and K. Vaughan, *Chem. Commun.*, 1272 (1967).



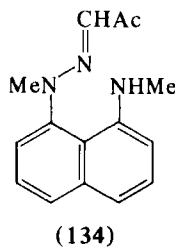
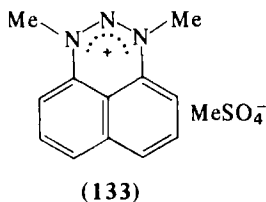
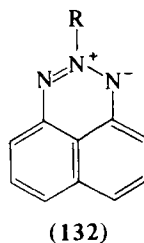
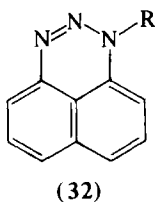
reaction with sulfuric acid, undergoes cyclization to the resonance-stabilized 14- π system (**128**, $\text{X} = \text{O}$, $\text{R}^1 = \text{Ph}$, $\text{R}^2 = \text{H}$), which can be isolated as the tetrafluoroborate salt. Repetition of this sequence of reactions with **39**, $\text{R} = \text{H}$, gives the fluoroborate salt of **128**, $\text{X} = \text{S}$, $\text{R}^1 = \text{H}$, $\text{R}^2 = \text{Ph}$. That alkylation of **10**, $\text{R} = \text{H}$, and of **39**, $\text{R} = \text{H}$, had given **127** and **129** respectively was demonstrated by reductive cleavage of the salts (**128**) with aqueous ethanol: **128**, $\text{X} = \text{O}$, $\text{R}^1 = \text{Ph}$, $\text{R}^2 = \text{H}$, gave 2,5-diphenyloxazole, while **128**, $\text{X} = \text{S}$, $\text{R}^1 = \text{H}$, $\text{R}^2 = \text{Ph}$, gave 2,4-diphenylthiazole.

Treatment of 3-aryl-4-imino-3,4-dihydro-1,2,3-benzotriazines (**67**) with sodium ethoxide and methyl iodide results in formation of a mixture of the isomeric methylated triazenes **130** and **131** by base-catalyzed



ring cleavage and methylation of the resultant ambident anion.¹²⁴ Methylation of the isomeric 4-arylamino-1,2,3-benzotriazines (56) with methyl iodide in ethanol followed by basification gives the betaines 80, $R = \text{Me}$.¹²⁵

Alkylation of 1*H*-naphtho[1,8-*de*]triazine (32, $R = \text{H}$) was originally believed to proceed exclusively at N_1 , but this is now known to be incorrect. Perkins showed in 1964 that treatment of 32, $R = \text{H}$, with either dimethyl or diethyl sulfate in ethanolic sodium hydroxide gives a 1 : 1 mixture of the N_1 - and N_2 -derivatives 32, $R = \text{Me}$, Et, and 132, $R = \text{Me}$, Et, respectively.⁶⁴ The structure of 132, $R = \text{Me}$, followed largely from



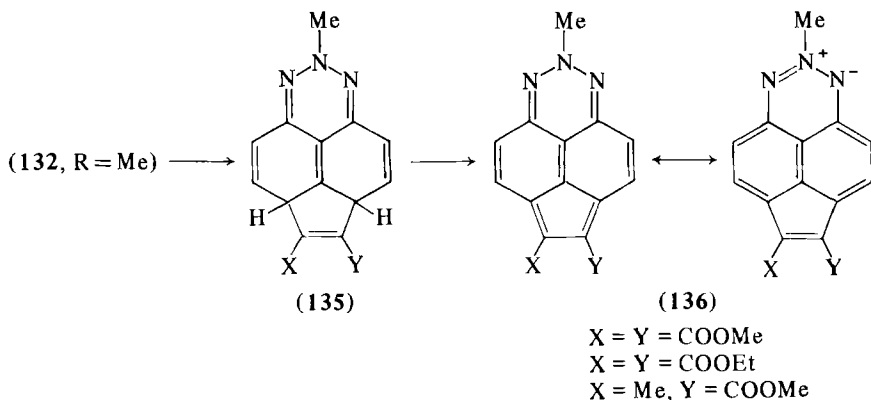
hydrogenolysis experiments: catalytic reduction gives a mixture of 1,8-diaminonaphthalene and methylamine. Perkins' results have subsequently been verified and extended by other workers, notably Tavs and his colleagues,^{126,127,155,156} who found that treatment of 32, $R = \text{H}$, with a wide range of dialkyl sulfates, alkyl tosylates, alkyl halides, and nitro-activated aryl halides in ethanolic sodium hydroxide resulted in each case in substitution at both N_1 and N_2 . Moreover, the N_2 -isomer (132) was found to be the major product in almost every instance. When dimethyl sulfate/potassium carbonate/acetone is used as the alkylating reagent, however, a mixture of 32, $R = \text{Me}$, 132, $R = \text{Me}$, 133, and the ring-cleaved product 134 is obtained.¹⁵⁷ The 1,3-dimethyl derivative (133) can also be obtained in virtually quantitative yield by treatment of 32, $R = \text{H}$, with dimethyl sulfate in benzene.

¹⁵⁵ H. Beecken, P. Tavs, and H. Sieper, *Liebigs Ann. Chem.* **704**, 166 (1967).

¹⁵⁶ H. Beecken and P. Tavs, *Liebigs Ann. Chem.* **704**, 172 (1967).

¹⁵⁷ H. Beecken, *Angew. Chem., Int. Ed. Engl.* **6**, 360 (1967).

The chemistry of betaines of the type **132** is as yet largely unexplored. Tavs *et al.* have investigated their reactions with alkyl, acyloxy, and nitrogen radicals and shown that substitution, addition, and dimerization occur via radical attack on the naphthalene ring system, although in most cases very low yields of products are obtained.^{155,156} Much more spectacular reactions have been described by Rees and his co-workers, who found that the 2-methylbetaine (**132**, R = Me) undergoes 1,11-dipolar cycloaddition reactions with acetylenic esters to give, after oxidation of the initial adducts **135**, either *in situ* or by addition of sulfur to the reaction mixture, the 2-methylacenaphtho[5,6-*de*]triazines (**136**).¹⁵⁸ This striking transformation represents the first example of a $12\pi + 2\pi$ cycloaddition reaction. The related aromatic system (**136**, X = Y = H) had previously been prepared by Perkins by methylation of acenaphtho[5,6-*de*]triazine (**92**), which gave a mixture of the N₁- and N₂-methyl derivatives **93**, R = Me, and **94**, R = Me, and subsequent oxidation of **94**, R = Me, with tetrachlorobenzoquinone.^{159,160}



As mentioned above, condensed 1,2,3-triazine derivatives can be arylated by treatment with nitro-activated aryl halides. The only other report of direct arylation of the 1,2,3-triazine system is due to McKillop and Kobylecki, who studied the reaction of 1,2,3-benzotriazin-4-one (**10**, R = H) with diaryliodonium salts in the presence of base. Treatment of **10**, R = H, with diphenyl- and di-*p*-bromophenyliodonium chloride results in exclusive arylation at N₂ and gives the corresponding triazinium betaines (**77**, R = Ph, *p*-BrC₆H₄) in good yield. When di-*p*-tolyliodonium chloride is used, a mixture of the N₂-, N₃-, and *O*-arylated

¹⁵⁸ C. W. Rees, R. W. Stephenson, and R. C. Storr, *J. Chem. Soc., Chem. Commun.*, 1281 (1972).

¹⁵⁹ A. R. J. Arthur, P. Flowerday and M. J. Perkins, *Chem. Commun.*, 410 (1967).

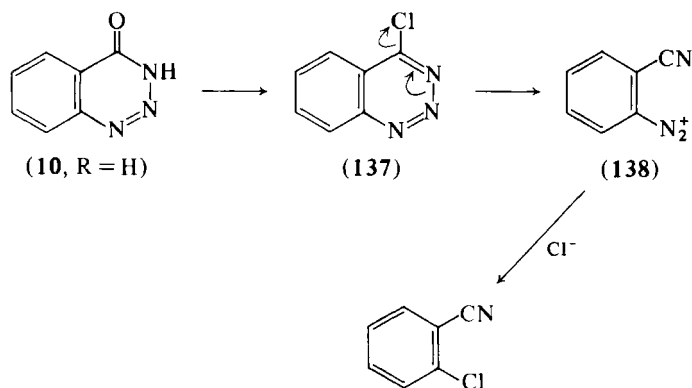
¹⁶⁰ P. Flowerday, M. J. Perkins, and A. R. J. Arthur, *J. Chem. Soc. C*, 290 (1970).

derivatives is obtained, while no reaction is observed with di-*p*-anisilyliodonium salts.^{117,118} These results are consistent with nucleophilic substitution of the iodonium salts by the anion of **10**, R = H.¹⁶¹

4. With Electrophiles and Nucleophiles

Most of the known types of reactions of condensed 1,2,3-triazines with both electrophiles and nucleophiles have necessarily been included in the appropriate preceding sections. The following brief discussion is therefore restricted to coverage of a number of reactions that have not so far been mentioned and, in most cases, have not been investigated in detail.

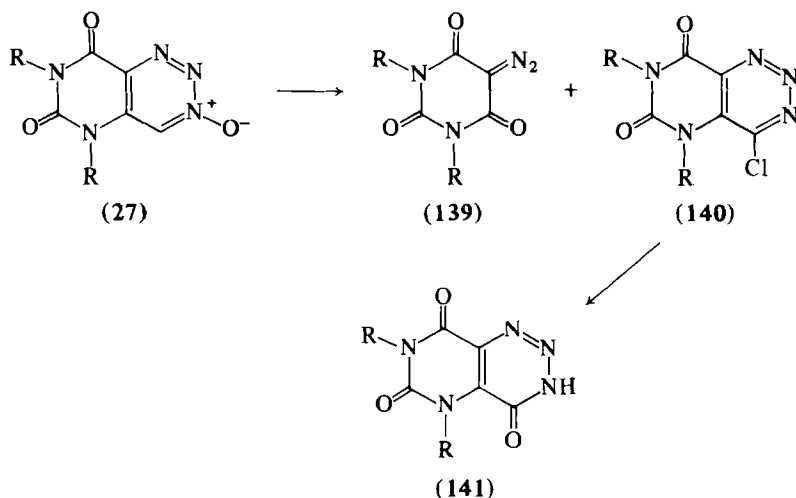
Condensed 4-halo-1,2,3-triazines are a virtually unknown class of compounds and are apparently very unstable. Reaction of 1,2,3-benzotriazin-4-one (**10**, R = H) with a mixture of phosphorus oxychloride and phosphorus pentachloride, for example, results in formation of *o*-chlorobenzonitrile, presumably via formation and then decomposition of the 4-chlorotriazine (**137**) to give the diazonium salt (**138**), subsequent



reaction of which with chloride ion gives the observed product.¹⁶² Treatment of the pyrimido[5,4-*d*]triazine 3-oxides (**27**, R = Me, Et) with thionyl chloride similarly gives unexpected results; the major product in each case is the 1,3-dialkyl-5-diazobarbituric acid (**139**, R = Me, Et) together with a small amount of the triazinones **141** (R = Me, Et).⁴⁹ The latter compounds were shown to arise via facile hydrolysis of the corresponding 4-chlorotriazines **140**, R = Me, Et, and **140**, R = Me was in fact isolated as an unstable solid. Reaction of 4-substituted 1,2,3-benzo-

¹⁶¹ F. M. Beringer and R. A. Falk, *J. Chem. Soc.*, 4442 (1964).

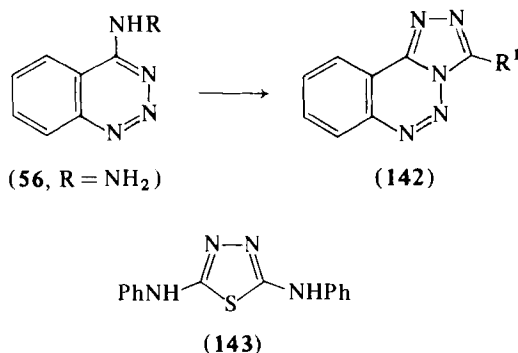
¹⁶² M. S. Gibson, *J. Chem. Soc.*, 3539 (1963).



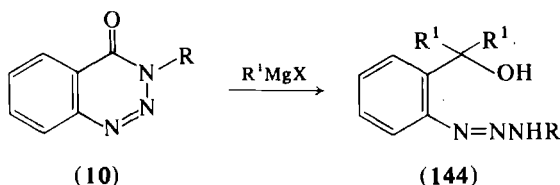
triazine 3-oxides (15, $R = \text{Me, Ph}$) with a mixture of phosphorus tri- and pentachloride has been shown to give the corresponding *o*-azido ketones.³⁵⁻³⁸

The reactions of 4-amino-1,2,3-benzotriazines with electrophilic reagents are generally predictable, although exceptions are known. Thus, treatment of 4-hydrazino-1,2,3-benzotriazine (56, $R = \text{NH}_2$) with diethoxymethyl acetate or cyanogen bromide gives the *s*-triazolo[4,3-*c*]triazines 142, $R^1 = \text{H, NH}_2$, respectively, while reaction with phenyl isocyanate gives the expected substituted semicarbazide 56, $R = \text{NHCONHPh}$. Reaction of 56, $R = \text{NH}_2$, with phenyl isothiocyanate, on the other hand, gives the 1,3,4-thiadiazole 143.¹³⁵

No detailed studies have been carried out on electrophilic substitution of the homocyclic ring(s) in condensed 1,2,3-triazine derivatives. Nitration and bromination of 3-phenyl-1,2,3-benzotriazin-4(3*H*)-one (10, $R =$



Ph) has been reported to proceed smoothly to give, as expected, the corresponding 3-(*p*-nitrophenyl) and 3-(*p*-bromophenyl) derivatives.¹⁶² Gibson found that the betaine (132, R = Me) dissolved in sulfuric acid to give a blue solution, a result which is consistent with sulfonation in the naphthalene ring system, and also reported that the same compound reacted smoothly with bromine in acetic acid to give a tetrabromo derivative in which all the bromine atoms were located in the naphthalene system. The structure of this compound was not, however, established.⁶⁴



The reactions of 3-substituted 1,2,3-benzotriazin-4(3*H*)-ones (10) with Grignard reagents have been investigated and shown to proceed in a predictable manner. The 3-aryl derivatives (10, R = aryl) give the carbinols (144, R = aryl) in generally excellent yields, while the 3-acetyl (10, R = COMe) and 3-benzoyl derivatives (10, R = C(=O)Ph) give the parent triazinone (10, R = H) together with trimethyl- and triphenylcarbinol, respectively. It has been claimed on the basis of the latter experiments that 10, R = H, is stable to the action of Grignard reagents.¹⁶³ The reactions of 4-methyl- and 4-phenyl-1,2,3-benzotriazine 3-oxide (15, R = Me, Ph) with phenylmagnesium bromide have also been studied, and in each case a complicated mixture of products was obtained. Very small amounts of a number of these products were isolated and characterized in each case, and their formation was rationalized in terms of nucleophilic addition of the reagent across the 1,4- and 3,4-positions and cleavage of the heterocyclic ring.¹⁶⁴

5. Thermal and Photochemical

Interest in the thermal and photochemical reactions of condensed 1,2,3-triazine derivatives dates from 1962, when first Gibson¹⁶⁵ and then Hey, Rees, and Todd¹⁶⁶ reported independently on the reactions of 3-phenyl-1,2,3-benzotriazin-4(3*H*)-one (10, R = Ph) at elevated

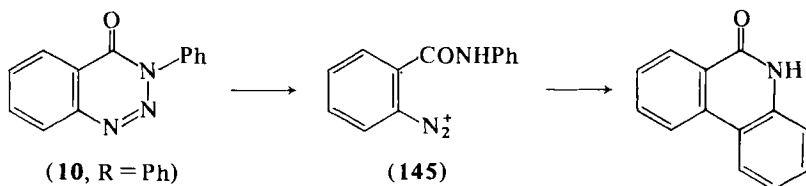
¹⁶³ A. Mustafa, W. Asker, A. M. Fleifel, S. Khattab, and S. Sherif, *J. Org. Chem.* **25**, 1501 (1960).

¹⁶⁴ H. Igeta, T. Tsuchiya, and T. Nakai, *Tetrahedron Lett.*, 3117 (1971).

¹⁶⁵ M. S. Gibson, *Chem. Ind. (London)*, 698 (1962).

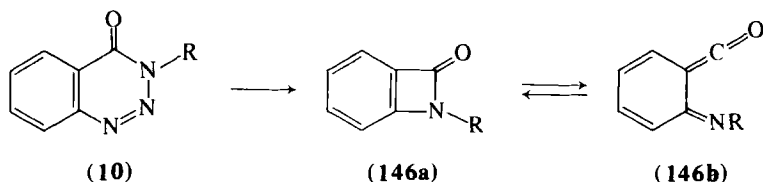
¹⁶⁶ D. H. Hey, C. W. Rees, and A. R. Todd, *Chem. Ind. (London)*, 1332 (1962).

temperatures. Gibson studied the decomposition of **10**, R = Ph, in syrupy phosphoric acid at 200–220°; he found that phenanthridone was formed in low (5–10%) yield together with phenol and salicylic acid and suggested that reaction proceeded via formation and decomposition of the diazonium salt (**145**). Decomposition of **10**, R = Ph, at temperatures



in excess of 250° and in the absence of solvent was shown by Hey, Rees, and Todd to give mainly acridone (31%) and phenanthridone (14%), and when liquid paraffin was employed as solvent in an attempt to modify the rather vigorous reaction, benzanilide was obtained in good yield. Consequently, it was suggested that under these latter conditions the reaction was probably free radical in nature.

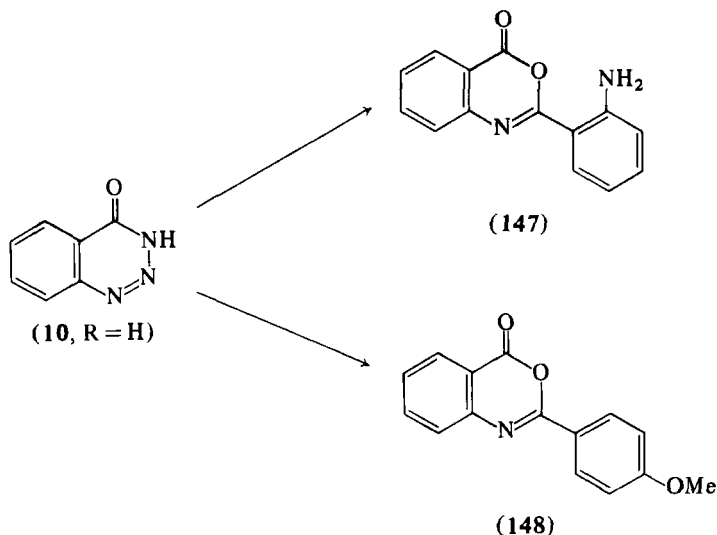
Much of the subsequent interest in these reactions was centered on the question of whether highly reactive intermediates such as **146** are generated during decomposition. High resolution mass spectral studies clearly reveal that for **10** loss of nitrogen and formation of species equivalent to **146** is one of the preferred fragmentation pathways (see Section II, D, 6), and it was tacitly assumed for some time that thermal



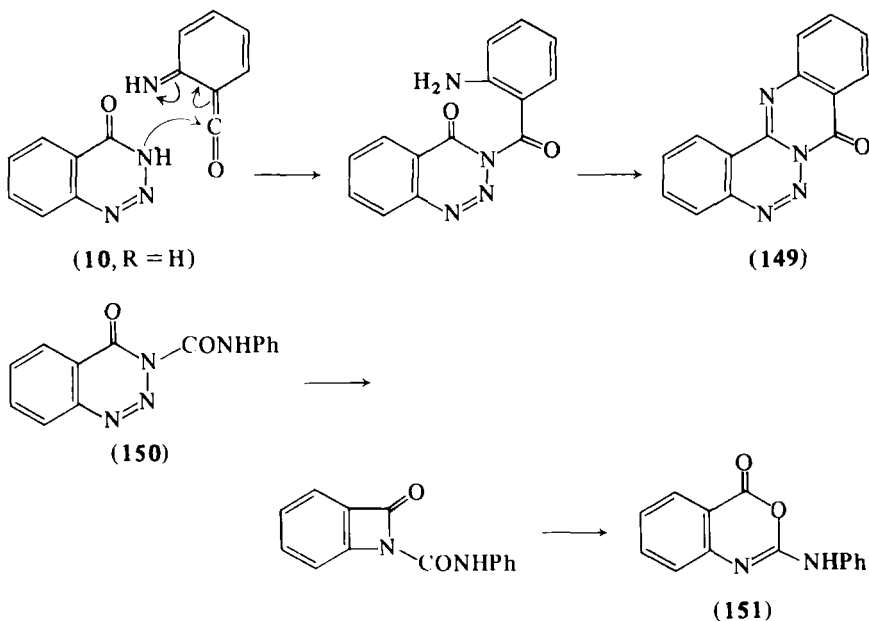
decomposition of these compounds proceeded similarly. Most of the data that were advanced in support of this assumption were not, however, unambiguous, and, while they were consistent with rational explanations for various proposed reaction pathways, they did not offer any proof either for the reaction pathways or for the intermediacy of **146**. Thus, **10**, R = H, has been shown to decompose thermally to give **147**,^{167,168} which can formally be regarded as the dimer of **146b**, R = H,

¹⁶⁷ R. K. Smalley, H. Suschitzky, and E. M. Tanner, *Tetrahedron Lett.*, 3465 (1966).

¹⁶⁸ J. G. Archer, A. J. Barker, and R. K. Smalley, *J. Chem. Soc. C*, 1169 (1973).



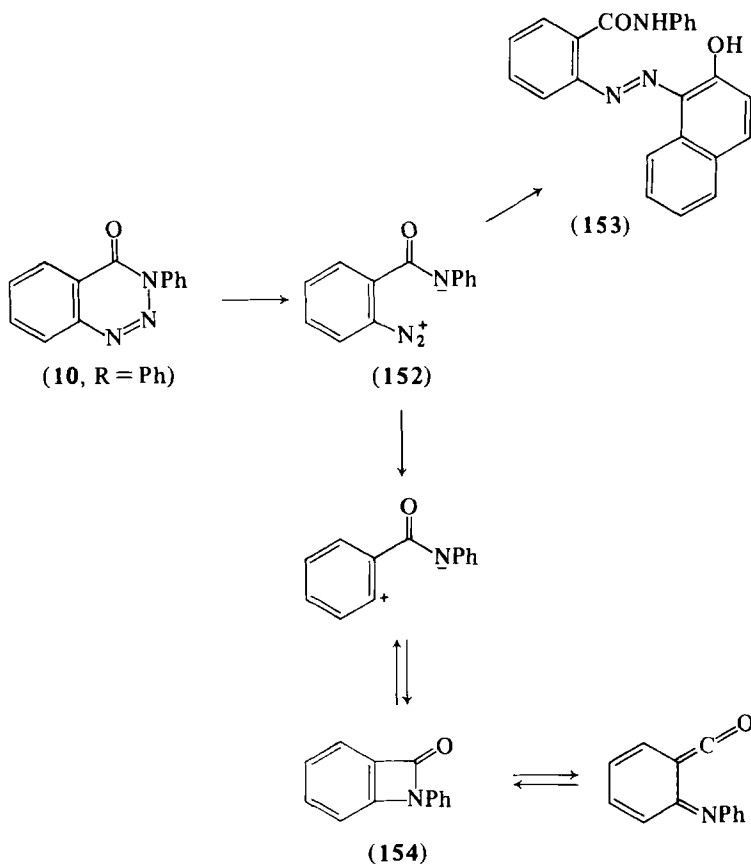
while the benzoxazone (148) and acridone can be isolated when the reaction is carried out in the presence of *p*-anisaldehyde and benzyne, respectively;¹⁶⁹ formation of both 148 and acridone can be rationalized on the basis of a cycloaddition reaction between the ketene-imine (146b, R = H) and the aldehyde carbonyl group or benzyne. Similarly, decom-



¹⁶⁹ H. E. Crabtree, R. K. Smalley, and H. Suschitzky, *J. Chem. Soc. C*, 2730 (1968).

position of **10**, R = H, in refluxing diethylene glycol dimethyl ether gives **149** in 70% yield, which can be explained in terms of reaction of **146b**, R = H with unchanged triazinone,¹⁷⁰ while thermolysis in the presence of phenyl isocyanate gives **151**.¹⁷¹ This latter reaction was originally interpreted in terms of addition of the isocyanate to the ketene-imine (**146b**, R = H), but is now believed to involve initial formation of the 3-phenylcarbamoyl-1,2,3-benzotriazin-4(3*H*)-one (**150**) and subsequent decomposition of this species as shown (**150** → **151**).¹⁶⁹

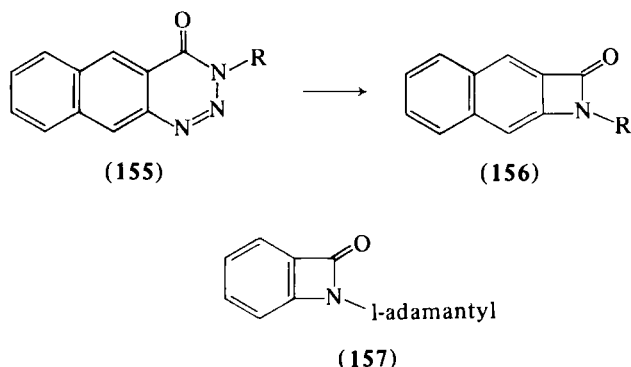
Results available from studies of the photochemical decomposition of benzotriazinones indicate that formation of the reactive species **146** during thermolysis of **10** is a reasonable postulate. Simple 3-alkyl-1,2,3-benzotriazin-4(3*H*)-ones (**10**, R = alkyl) are apparently inert to photo-



¹⁷⁰ A. W. Murray and K. Vaughan, *J. Chem. Soc. C*, 2070 (1970).

¹⁷¹ H. Herlinger, *Angew. Chem., Int. Ed. Engl.* **3**, 378 (1964).

lysis,¹⁷² but irradiation of the 3-aryl derivatives (10, R = aryl) results in loss of nitrogen and formation of the reactive intermediate (146, R = aryl). The overall reaction pathway depends upon the nature of the medium used, and most of the mechanistic details have been supplied by Ege and his collaborators.¹⁷²⁻¹⁷⁴ Photolysis of 3-phenyl-1,2,3-benzotriazin-4(3*H*)-one (10, R = Ph), for example, has been shown to proceed via initial formation of the diazonium salt (152), which can be trapped as the azo dye (153) by reaction with β -naphthol. Loss of nitrogen from 152 leads to 154, from which the ultimate products are derived. Thus, when nucleophilic solvents such as alcohols are employed, photolysis gives *N*-phenylanthranilic esters; addition of other nucleophiles to the medium results in formation of analogous products via reaction with the intermediate 154.^{172,173,175,176} Acridone and phenanthridone are formed when photolysis is carried out in the absence of any nucleophilic species, e.g., in anhydrous acetone.^{173,175} The results obtained by Ege are fully consistent with those from ¹⁵N labeling studies.¹⁷⁴



While all the above results on the thermolysis and pyrolysis of fused triazinones can readily be accommodated on the basis of formation of a reactive species (146), it is only recently that unambiguous evidence for such intermediates has been provided. Ege *et al.*^{117,178} found that photolysis of the naphthotriazinone 155, R = Ph, gives the *N*-phenylnaphth[2,3-*b*]azet-2(1*H*)-one (156, R = Ph) as an isolable, moderately stable solid. Bashir and Gilchrist have shown that photolysis

¹⁷² G. Ege and E. Beisiegel, *Angew. Chem.* **77**, 723 (1965).

¹⁷³ G. Ege, *Chem. Ber.* **101**, 3079 (1968).

¹⁷⁴ G. Ege, *Chem. Ber.* **101**, 3089 (1968).

¹⁷⁵ E. M. Burgess and G. Milne, *Tetrahedron Lett.*, 93 (1966).

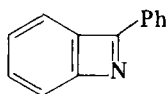
¹⁷⁶ S. African Patent 71 00,512 [CA **76**, 140237 (1971)].

¹⁷⁷ G. Ege and E. Beisiegel, *Angew. Chem.* **80**, 316 (1968).

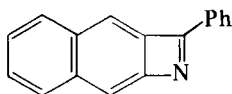
¹⁷⁸ C. Wunsche, G. Ege, E. Beisiegel, and F. Pasedach, *Tetrahedron* **25**, 5869 (1969).

of **155**, $R = NH_2$, similarly gives the fused azetone **156**, $R = NH_2$, as an isolable, crystalline solid, and they have also described the preparation of **157** by pyrolysis of 3-(1-adamantyl)-1,2,3-benzotriazin-4(3*H*)-one at 600° .¹⁷⁹ The benzazetone **157** is remarkably stable thermally, but, like **156**, $R = Ph, NH_2$, reacts readily with nucleophiles to give products derived by opening of the four-membered ring. Indeed, the properties of **156**, $R = Ph, NH_2$, and **157**, insofar as they have been studied, are fully compatible with those of the reactive species generated during thermolysis and photolysis of simple fused triazinones.

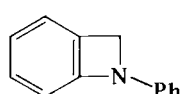
Vapor-phase flash pyrolysis of 4-phenyl-1,2,3-benzotriazine (**8**, $R = Ph$) at 420° – 450° gives a mixture of biphenylene, 9-phenylacridine, unchanged triazine, and the 2-phenylbenzazete (**158**).¹⁸⁰ Compound **158**, which is stable at -80° , dimerizes when warmed to room temperature and reacts readily with nucleophiles and 1,3-dienes. The thermally more



(158)

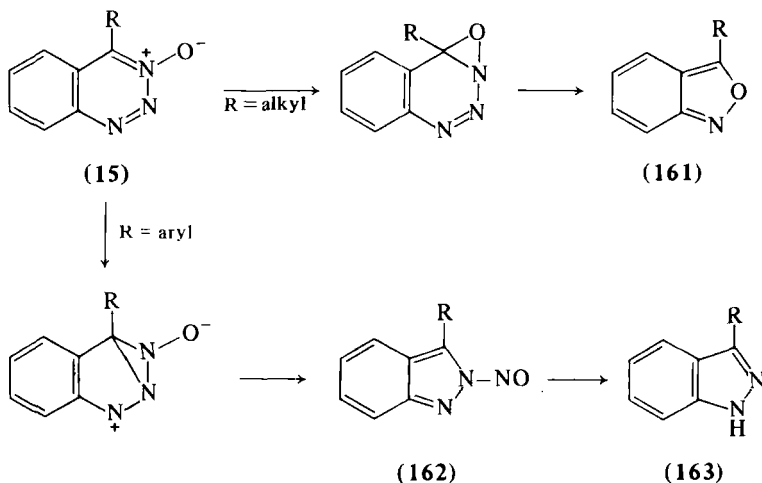


(159)



(160)

stable naphthalene analog (**159**) has been prepared similarly from the corresponding 4-phenyl-1,2,3-naphtho[2,3-*d*]triazine. Photolysis of 3-phenyl-3,4-dihydro-1,2,3-benzotriazine (**29**, $R = Ph$) also results in loss of nitrogen, and *N*-phenylbenzazetine (**160**) is formed in 50% yield.¹⁸¹

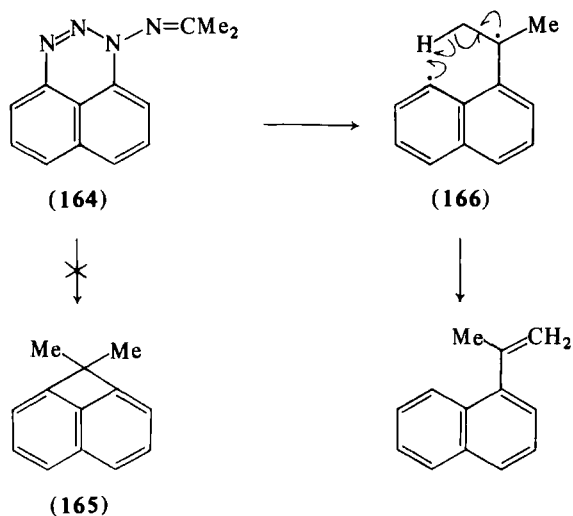


¹⁷⁹ N. Bashir and T. L. Gilchrist, *J. Chem. Soc., Perkin Trans. I*, 868 (1973).

¹⁸⁰ B. M. Adger, M. Keating, C. W. Rees, and R. C. Storr, *J. Chem. Soc., Chem. Commun.*, 19 (1973).

¹⁸¹ E. M. Burgess and L. McCullagh, *J. Amer. Chem. Soc.* **88**, 1580 (1966).

The photochemical behavior of a variety of 4-substituted 1,2,3-benzotriazine 3-oxides has been studied by Horspool *et al.*¹⁸² The 4-alkyl derivatives (15, R = Me, Et) undergo elimination of nitrogen and give 3-alkylanthranils (161, R = Me, Et) in excellent yield, together with small amounts of *o*-aminoacetophenone and *o*-aminopropiophenone, respectively. Photolysis of the 4-aryl derivatives (15, R = Ph, *p*-MeOC₆H₄, *p*-ClC₆H₄), on the other hand, gives the corresponding 3-arylindazoles (163) in good yield, together with small amounts of 2-azidophenyl aryl ketones and 3-arylbenzisoxazoles. Formation of the indazoles (163) has been interpreted in terms of generation of the *N*-nitroso derivatives (162) followed by photochemical extrusion of nitric oxide.

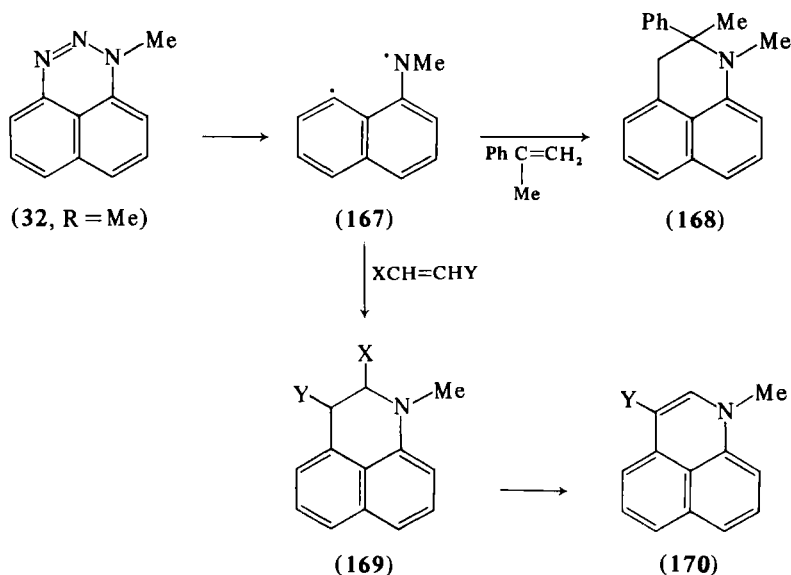


Burgess *et al.* have studied the photochemical behavior of 1-isopropylideneaminonaphtho[1,8-*de*]triazine (164) in an attempt to synthesize the highly strained hydrocarbon 165.¹⁸³ The triazine (164) decomposed with loss of nitrogen when irradiated in benzene; the product which was obtained, in 60% yield, was not 165, however, but 1-isopropylidenenaphthalene. The preferred reaction pathway for the intermediate 1,4-diradical (166) is thus by 1,6-hydrogen shift rather than intramolecular radical coupling. Interestingly, attempts to prevent the 1,6-hydrogen shift by use of the hexafluoroisopropylidene derivative were unsuccessful; irradiation of this compound resulted only in production of polymeric material.

¹⁸² W. M. Horspool, J. R. Kershaw, A. W. Murray, and G. M. Stevenson, *J. Amer. Chem. Soc.* **95**, 2390 (1973).

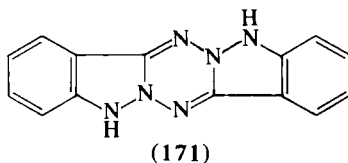
¹⁸³ E. M. Burgess, R. Carithers, and L. McCullagh, *J. Amer. Chem. Soc.* **90**, 1923 (1968).

Photolysis of 1-methylnaphtho[1,8-*de*]triazine (**32**, R = Me) also results in extrusion of nitrogen and formation of a diradical intermediate (**167**).^{184,185} Thus, reaction in cyclohexane as solvent gives, among other products, bicyclohexyl and 1-methylaminonaphthalene, while 8-phenyl-1-methylaminonaphthalene is the only product formed when benzene is used as solvent. Photochemical decomposition of **32**, R = Me, in the presence of olefins results in an unusual ring transformation, and with α -methylstyrene, for example, the triazine is converted into the dihydroazaphenalene derivative (**168**). When vinyl bromide and *trans*-



1,2-dichloroethane are used to trap the diradical (**167**), the intermediate dihydroazaphenalene derivatives (**169**, X = Br, Y = H, X = Y = Cl) undergo spontaneous dehydrohalogenation to give the azaphenalenes (**170**, Y = H, Cl). The related 1-methylacenaphtho[1,8-*de*]triazine behaves similarly on photolysis in the presence of olefins.

Photolysis of 4-azido-1,2,3-benzotriazine (**8**, R = N₃) is reported to give the pentacyclic compound **171**, but no mechanism for this conversion has been suggested.¹³⁵



¹⁸⁴ P. Flowerday and M. J. Perkins, *J. Amer. Chem. Soc.* **91**, 1035 (1969).

¹⁸⁵ P. Flowerday and M. J. Perkins, *J. Chem. Soc. C*, 298 (1970).

D. THEORETICAL, CRYSTALLOGRAPHIC, AND SPECTROSCOPIC ANALYSES

1. Molecular Structure

The molecular orbital structure of 1,2,3-benzotriazine has been calculated using the Hückel method, and the energy levels, charge densities, and wave functions were obtained.¹⁸⁶ Theoretically the charge densities thus obtained should be of some value in predicting the positions of electrophilic and nucleophilic attack, but in the absence of information on reagents and reaction conditions, such predictions cannot be made with any degree of accuracy.

2. X-Ray Crystallography

There are only three reports of X-ray crystallographic analyses of 1,2,3-triazine derivatives, namely of 4,5,6-tri-(*p*-methoxyphenyl)-triazine,¹⁴ 3-phenyl-1,2,3-benzotriazin-4(3*H*)-one and 1,2,3-benzotriazin-4(3*H*)-one, and the first of these has been discussed previously (see p. 218). The structure of 3-phenyl-1,2,3-benzotriazin-4(3*H*)-one (**10**, R = Ph) has been examined goniometrically and by Laue and rotating crystal methods and found to be as follows. The crystal is orthorhombic with the symmetry element mmm (Laue), where $a = 23.97$, $b = 9.06$, and $c = 5.37$ Å ($Z = 4$). The probable space group was identified as D_2^3 -P22₁2₁, but it was not possible to positively distinguish between this and the space groups D_2^3 -P22₁2₁ or D_2^1 -P222.¹⁸⁷

The crystal structure of 1,2,3-benzotriazin-4-one (**10**, R = H) has been determined recently by Hjortas, and the structural details obtained by the symbolic addition method in the Okl projection.¹⁸⁸ The space group was shown to be P2₁2₁2₁, with $a = 3.802(2)$, $b = 7.712(3)$, and $c = 22.213(8)$ Å ($Z = 4$). Hjortas' detailed structural investigation has proved to be particularly instructive and has provided a number of interesting facts about molecular geometry and electronic distribution. Thus, the benzene ring, as expected, is planar, but the triazinone ring adopts a slight boat conformation in which both N₁ and C₄ lie slightly above a plane through N₂, N₃, C₉, and C₁₀. Molecular dimension calculations reveal that complete delocalization of the π -electrons does not occur throughout the whole system, but only in the benzene ring. The N₁—N₂ bond is almost a pure N=N double bond (1.274 Å observed versus 1.26 Å calculated), while the N₂—N₃ bond is shorter than a normal N—N single bond (1.382 Å observed versus 1.46 Å

¹⁸⁶ S. C. Wait and J. W. Wesley, *J. Mol. Spectrosc.* **19**, 25 (1966).

¹⁸⁷ M. Grabowski, *Bull. Soc. Sci. Lett. Lodz* **11**, 3 (1960) [*CA* **55**, 18240 (1961)].

¹⁸⁸ J. Hjortas, *Acta Crystallogr. Sect. B* **29**, 1916 (1973).

calculated). Hence there is some degree of delocalization in the heterocyclic ring, and this is also evident from the N_3-C_4 (1.374 Å observed versus 1.45 Å calculated) and N_1-C_9 (1.402 Å observed versus 1.45 Å calculated) bond lengths. The results of bond angle generalization calculations indicate that the hydrogen atom in the heterocyclic ring is located at N_3 , not at N_1 or on oxygen.

3. Infrared Spectroscopy

The IR spectra of 1,2,3-triazine derivatives are unexpectedly complicated, and very few of the absorption bands for individual compounds have been unambiguously assigned. No systematic studies on these compounds have yet been reported and, for example, no assignments for the N—N—N fragment of the heterocyclic ring have yet been made. Consequently, IR spectroscopy has proved to be of relatively little use in structural elucidation work and has generally been applied only as a means of confirming the presence or the absence of particular, readily identifiable functional groups in individual compounds. Most of the IR data available on 1,2,3-triazine derivatives refer to the carbonyl stretching frequencies in 3-substituted 1,2,3-benzotriazin-4(3*H*)-ones. The observed frequencies are unexceptional and typical values for representative derivatives are summarized in Table I.

The IR spectra of 4-aryl- and 4-arylalkylamino-1,2,3-benzotriazines (68) are reported to show a characteristic band in the region 1135–1165 cm^{-1} . The origin of this absorption is not known, but apparently it can be of some utility in structure confirmation, as there is no similar band in

TABLE I
CARBONYL STRETCHING FREQUENCIES ($\nu_{C=O}$) FOR 3-SUBSTITUTED
1,2,3-BENZOTRIAZIN-4(3*H*)-ONES (10)

R	$\nu_{C=O}(\text{cm}^{-1})$	References
H	1685 1695	162 117, 147
Alkyl	1660–1685	122, 162, 189
Aryl	1660–1690	117, 162, 189, 190
COMe	1695, 1655	147
COPh	1718, 1690	147
CONHPh	1740, 1690	169
NH ₂	1670–1700	39
SO ₂ Cl	1695	95

¹⁸⁹ A. C. Mair and M. F. G. Stevens, *J. Chem. Soc. C*, 2317 (1971).

¹⁹⁰ M. Davis and F. G. Mann, *J. Chem. Soc.*, 945 (1962).

the IR spectra of the isomeric 3-aryl- and 3-arylalkyl-3,4-dihydro-4-imino-1,2,3-benzotriazines (67).⁹⁰

4. Nuclear Magnetic Resonance Spectroscopy

NMR spectroscopy has been little used in the 1,2,3-triazine field and, like IR spectroscopy, is useful only for confirmation of the presence of specific substituent groups.^{90,116,124,125} Attempts to extend this technique to more demanding problems, such as the site of alkylation¹²² or arylation^{117,118} of 1,2,3-benzotriazin-4(3*H*)-one, have been unsuccessful.

5. Ultraviolet Spectroscopy

There has been little systematic study of the UV spectra of condensed 1,2,3-triazine derivatives, but even so the technique has occasionally proved to be of some value in the solution of certain structural problems (see p. 234 and references 90, 117, 118, 125, 147, 191). Different classes of triazine derivatives give rise, as expected, to spectra that are characteristic of the basic chromophores and, while substituent effects have been noted within individual groups of compounds, confirmation of the structure of a given compound is sometimes possible on the basis of the UV spectrum.

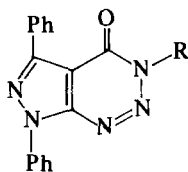
The UV spectrum of 1,2,3-benzotriazin-4-one (**10**, R = H) consists of two maxima at 223 nm ($\log \epsilon = 3.28$) and 278 nm ($\log \epsilon = 2.77$)¹⁶² and the spectra of a wide variety of 3-alkyl derivatives have been found to be closely similar, with maxima in the ranges 226–244 nm ($\log \epsilon = 4.33$ –4.49) and 284–289 nm ($\log \epsilon = 3.71$ –4.03), although only the longer wavelength absorption had been quoted for some compounds. The spectra of the 3-aryl derivatives are also similar to that of **10**, R = H,^{88,89} but significant substituent effects have been noted which depend on the position of the substituent (Me, Ph, MeO, MeCONH, Cl, NO₂) in the 3-aryl group.⁸⁸ Thus, relative to **10**, R = Ph, the spectra of the *o*-substituted phenyl derivatives show a strong hypsochromic shift and those of the *p*-substituted phenyl derivatives show a weak bathochromic shift; there is, however, virtually no substituent effect for the *m*-substituted phenyl derivatives. These effects are almost identical to those found in substituted benzanilides.

The UV spectra of other types of 1,2,3-triazine derivatives are generally more complicated than those of the 3-alkyl- and 3-aryl-1,2,3-benzotriazin-4(3*H*)-ones, and in most cases data are available for only a small number of compounds of each type. Consequently, the utility of this information in diagnostic and structural elucidation work is not very

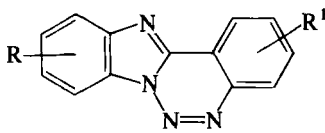
¹⁹¹ M. F. G. Stevens, *J. Chem. Soc. C*, 1096 (1967).



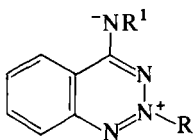
(172)



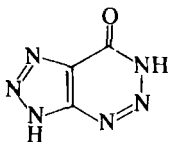
(173)



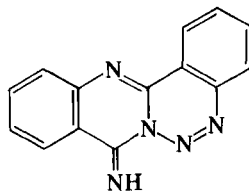
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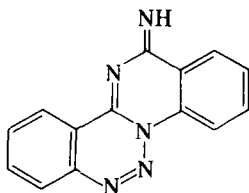
(175)



(176)



(177)



(178)

substantial. Spectral data have been reported for the 4-substituted 1,2,3-benzotriazine 3-oxides **15**, $R = \text{Me, Ph}$,¹⁸² and **20**⁴³; for a number of 4-alkyl- and 4-arylamino-1,2,3-benzotriazines (**56**, $R = \text{alkyl, aryl}$)^{90,100}; for a variety of 3-substituted 3,4-dihydro-4-imino-1,2,3-benzotriazines (**172**, $R = \text{alkyl, aryl}$; $R^1 = \text{H, alkyl, aryl}$)^{90,100,125}; for the pyrazolotriazines (**173**, $R = \text{H, Me}$)¹⁶²; for a number of benzimidazotriazines (**174**, $R, R^1 = \text{H, Cl, F, Me}$)¹⁰⁶; and for a variety of triazinium betaines (**76, 77, 79**,¹¹⁵⁻¹¹⁸ and **175**, $R = \text{alkyl, } R^1 = \text{aryl}$).¹²⁵ The spectra of 3-phenyl-3,4-dihydro-1,2,3-benzotriazine (**29**, $R = \text{Ph}$),¹⁹² 3-acetyl- and 3-benzoyl-1,2,3-benzotriazin-4(3*H*)-one (**10**, $R = \text{COMe, COPh}$),¹⁴⁷ 4-methylthio-1,2,3-benzotriazine,⁹⁰ **176**,¹⁹³ **177**,^{100,191} and **178**¹⁹¹ have also been recorded.

6. Mass Spectroscopy

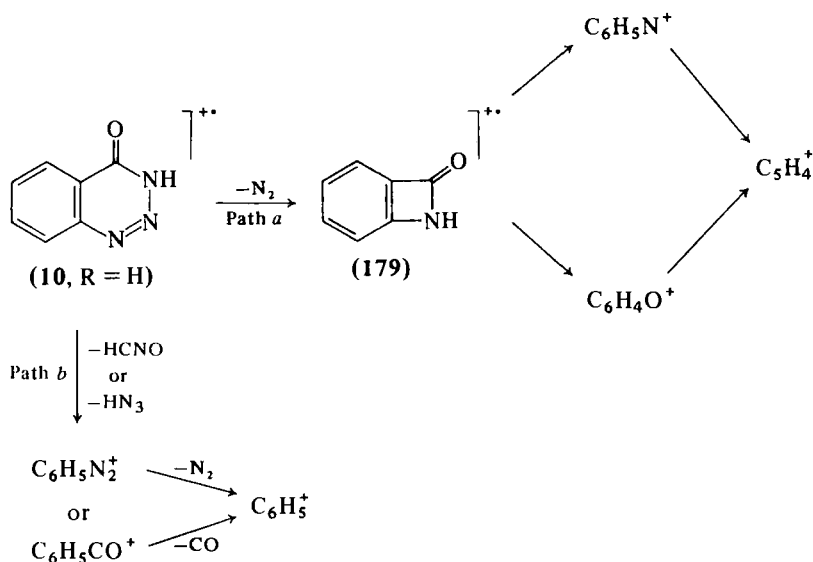
The mass spectra of a substantial number of 1,2,3-triazine derivatives of different types have recently been examined in some detail. The fragmentation patterns observed for the different compounds are, with

¹⁹² P. Ramart-Lucas and J. Hoch, *Bull Chim. Soc. Fr.*, 447 (1949).

¹⁹³ Y. F. Shealy, R. F. Struck, L. B. Holum, and J. A. Montgomery, *J. Org. Chem.* **26**, 2396 (1961).

few exceptions, remarkably similar and to a large extent, predictable. Consequently, mass spectroscopy should prove to be increasingly useful not only in confirmation of structure, but also in the investigation of compounds of unusual structure.

Two major fragmentation pathways have been observed in the mass spectrum of 1,2,3-benzotriazin-4-one (**10**, $R = H$), and these are outlined in Scheme 1.¹⁹⁴ The primary mode of cleavage (Path *a*) involves loss of nitrogen and formation of the β -lactam (**179**), which undergoes further fragmentation as shown. Alternatively, loss of HCNO or HN_3 (Path *b*) leads to a diazonium ion or acylium radical ion which then decomposes to $C_6H_5^+$ by loss of nitrogen or carbon monoxide. The mass



SCHEME 1

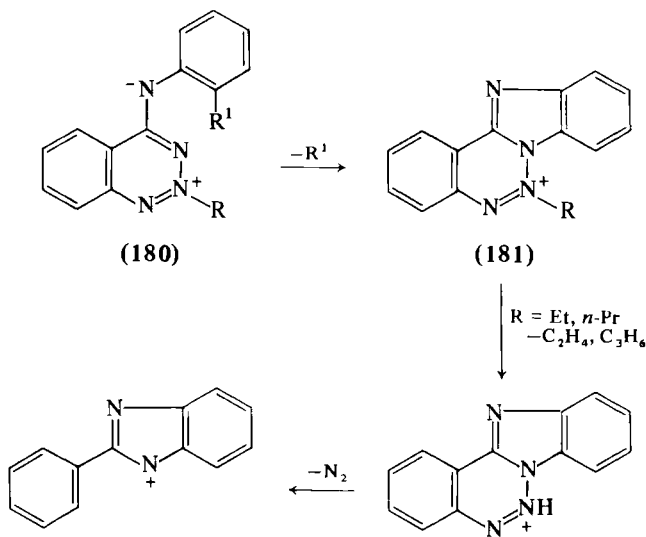
spectral fragmentation patterns of other nuclear substituted 1,2,3-benzotriazin-4(3*H*)-ones are essentially similar to that of **10**, $R = H$,¹⁶⁸ as are those of a variety of 3-alkyl-^{194,195} and 3-aryl-1,2,3-benzotriazin-4(3*H*)-ones,^{178,195} and minor variations can normally be readily explained. Elimination of formaldehyde from **10**, $R = CH_2OH$, for instance, is the expected McLafferty rearrangement, and the remainder of the spectrum corresponds to fragmentation of the derived **10**, $R = H$.¹⁹⁴

¹⁹⁴ J. C. Tou, L. A. Shadoff, and R. H. Rigterink, *Org. Mass. Spectrom.* **2**, 355 (1969).

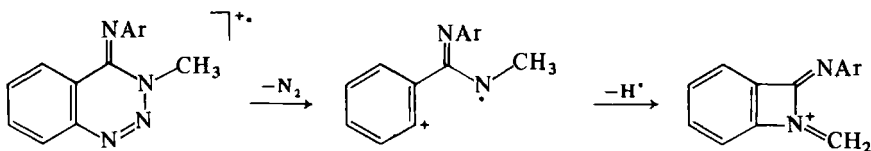
¹⁹⁵ R. A. W. Johnstone, D. W. Payling, P. N. Preston, H. N. E. Stevens, and M. F. G. Stevens, *J. Chem. Soc. C*, 1238 (1970).

In contrast to the situation outlined in Scheme 1 for simple benzotriazinones, fragmentation of the naphthotriazinone **155**, $R = Ph$, under electron impact does not lead to the corresponding naphthazetone (**156**, $R = Ph$). Nitrogen is lost from **155**, $R = Ph$, but comparison of appearance potential measurements for this compound and genuine **156**, $R = Ph$, reveals that the latter species is not formed during the fragmentation of the naphthotriazinone.¹⁷⁷ The major ions formed in the fragmentation of the aminonaphthotriazinone **155**, $R = NH_2$, are at m/e 212 (parent ion), 184 ($P-N_2$ or CO), 155 ($P-HCN_2O$ or HN_4) and 127 (the naphthyl radical ion).

Mass spectroscopy has been widely used in studies on the triazinium betaines **76**,¹¹⁶⁻¹¹⁸ **77**,¹¹⁶⁻¹¹⁸ **81**,¹²² and **180**.^{125,195} The mass spectra of **76** and **77** provided supporting evidence for the assigned structures of the two classes of betaines and also allowed ready distinction to be made between them. The most notable contrast between the mass spectra of **76** and **77** is the presence of a very intense parent peak for the latter compounds and the almost total absence of a parent peak for the *N*-oxides (**76**). All the compounds **76** underwent fragmentation to give prominent ions at m/e values corresponding to $P-O$, $P-(N_2 \text{ or } CO)$, $P-O-(N_2 \text{ or } CO)$, $RC_6H_4N_3O^+$, $RC_6H_4N_2^+$, $RC_6H_4^+$, and $C_7H_4O^+$ or $C_6H_4N_2^+$. In addition to a prominent parent peak, the spectra of compounds **77** showed prominent ions at m/e values corresponding to $P-(N_2 \text{ or } CO)$, $P-N_2-CO$, $RC_6H_4N_2^+$, $RC_6H_4^+$, and $C_7H_4O^+$ or $C_6H_4N_2^+$. The relative intensities of the various prominent ions were



SCHEME 2

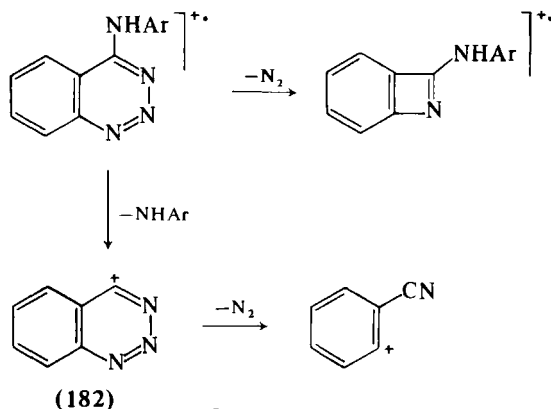


SCHEME 3

reasonably consistent within each group of related compounds, but they differed by a factor of 2–3 between the groups. The mass spectra of the betaines **79** and **81** have been studied in less detail and primarily for the purpose of distinguishing between **79** and **81** and the isomeric 3-substituted 1,2,3-benzotriazinones and triazinethiones.

Fragmentation of the betaines **180**, $R = \text{Me, Et, } n\text{-Pr, } i\text{-Pr}$; $R^1 = \text{Cl, NO}_2, \text{CN}$, has been shown to proceed by intramolecular displacement of the *o*-substituent of the *N*-aryl group and formation of the tetracyclic systems **181** as shown in Scheme 2.^{125,195} The subsequent breakdown pattern shown in Scheme 2 was observed for **181**, $R = \text{T}$ and **181**, $R = n\text{-Pr}$, but not for **181**, $R = \text{Me}$, where elimination of methylene would be necessary; compounds **180**, $R = \text{Me, } R^1 = \text{NO}_2$; $R^1 = \text{CN}$, underwent fragmentation by loss of CH_3N_2 from the tetracyclic species **181**, $R = \text{Me}$. In all, seven different compounds were examined in this study and the differences noted in their fragmentation patterns assigned to the relative ease of elimination of Cl , NO_2 , or CN . All the compounds showed prominent ions at m/e values corresponding to $\text{C}_7\text{H}_4\text{N}^+$ and $\text{C}_6\text{H}_4\text{N}^+$.

The mass spectra of a number of 3-aryl-3,4-dihydro-4-imino-1,2,3-benzotriazines (**172**) have been recorded and found to be similar to those of 1,2,3-benzotriazinones, i.e., initial fragmentation with loss of nitrogen. 3-Alkyl-3,4-dihydro-4-arylimino-1,2,3-benzotriazines show an



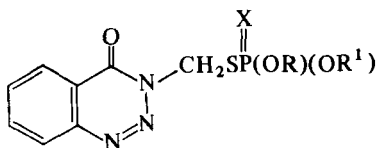
SCHEME 4

intense peak in their mass spectra corresponding to loss of HN_2 from the molecular ion, which can be rationalized as shown in the example in Scheme 3. 4-Arylamino-1,2,3-benzotriazines fragment with loss of the 4-substituent, and the ion at m/e 130 (182) is intense (Scheme 4).¹⁹⁵

E. USES

1. Insecticides

Many simple 3-substituted 1,2,3-benzotriazin-4(3*H*)-ones of the type 126 have been found to possess insecticidal properties and are of considerable commercial importance. They are readily prepared (see p.



(126, X = O, S)

248), and variation of X (O or S) and R^1 and R^2 is a synthetically trivial operation. The derivative 126, X = S, $\text{R}^1 = \text{R}^2 = \text{Et}$, was found to be particularly efficacious against bollworms and other cotton insects in initial studies; since then, various derivatives have been employed, with a variety of synergists,^{196–198} most importantly against cotton insects^{199–201} and cotton fungal diseases;²⁰² against both insects and

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¹⁹⁷ E. E. Nelson, B. A. Croft, A. J. Howitt, and A. L. Jones, *Environ. Entomol.* **2**, 219 (1973).

¹⁹⁸ J. F. Kreitzer and J. W. Spann, *Bull. Environ. Contam. Toxicol.* **9**, 250 (1973) [*CA* **79**, 28115 (1973)].

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²⁰⁰ C. B. Cowan, J. W. Davis, and C. R. Parencia, *J. Econ. Entomol.* **50**, 663 (1957).

²⁰¹ C. R. Parencia, C. B. Cowan, and J. W. Davis, *J. Econ. Entomol.* **50**, 666 (1957); T. R. Pfrimmer, *ibid.* **51**, 41 (1958); A. A. M. Kamel, A. Shueb, A. Hanna, and S. Soliman, *Agr. Res. Rev.* **36**, 1 (1958) [*CA* **53**, 12571 (1959)]; P. L. Adkisson, L. H. Wilkes, and S. P. Johnson, *Texas Agr. Sta. Bull.* **920** (1958) [*CA* **53**, 12572 (1959)]; E. Rivnay and S. Yathom, *Ktavim* **9**, 3 (1958) [*CA* **53**, 13493 (1959)];

fungus diseases on tobacco;²⁰³ on vegetables, such as *Brassica*,^{204–206} corn,²⁰⁷ potatoes,²⁰⁸ onions,²⁰⁹ and beans;²¹⁰ on fruits such as

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pineapples,²¹¹ apples,^{197,212} citrus fruits,²¹³ grapes,²¹⁴ peaches,²¹⁵ currants,²¹⁶ apricots,²¹⁷ tomatoes,²¹⁸ and nuts,²¹⁹ and on other miscellaneous fruit and vegetables.²²⁰ A wide variety of other derivatives has been employed as insecticides and fungicides for more general use.^{205, 221-223}

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- ²²⁴ W. J. Mistic and D. F. Martin, *J. Econ. Entomol.* 49, 757 (1956).

The toxicology and pharmacology of esters of the type 126 have been studied in some detail, both because of their commercial importance and their close structural relationship to some nerve gases.^{198,224-232} They are poisonous compounds²²⁷⁻²³⁴ which act, like the related alkyl dithionophosphate esters,^{231,233,235} by cholinesterase inhibition, and their misuse has been associated with certain mental disorders.²³⁶ As a consequence of this pronounced biological activity, much attention has been directed to both the detection and isolation of the compounds as such,²³⁷

- ²²⁵ K. P. Dubois, D. R. Thursh, and S. D. Murphy, *J. Pharmacol. Exp. Therap.* **119**, 208 (1957) [CA 51, 10739 (1957)].
- ²²⁶ J. W. Cook, J. R. Blake, G. Yip, and M. Williams, *J. Ass. Offic. Agr. Chem.* **41**, 399 (1958) [CA 52, 16436 (1958)].
- ²²⁷ S. D. Murphy and K. P. Dubois, *J. Pharmacol. Exp. Therap.* **124**, 194 (1958) [CA 53, 2301 (1959)].
- ²²⁸ C. B. Shaffer and B. West, *Toxicol. Appl. Pharmacol.* **2**, 1 (1960) [CA 54, 9117 (1960)].
- ²²⁹ T. B. Gaines, *Toxicol. Appl. Pharmacol.* **2**, 88 (1960) [CA 54, 9119 (1960)].
- ²³⁰ N. Motoyama and W. C. Dauterman, *Pestic. Biochem. Physiol.* **2**, 170 (1972) [CA 78, 12416 (1973)]; S. M. Z. Naqvi, *J. Econ. Entomol.* **66**, 70 (1973); A. R. Thompson and F. L. Gore, *ibid.* **65**, 1248 (1972); P. D. Lingren, D. A. Wolfenbarger, J. B. Nosky, and M. Diaz, *ibid.* **65**, 1295 (1972).
- ²³¹ T. E. Shellenberger, B. J. Gough and L. A. Escuriex, *Pestic. Symp. Collect. Pap. Inter-Amer. Conf. Toxicol. Occup. Med., 6th-7th Meetings*, 205 (1968-1970) [CA 79, 74639 (1973)].
- ²³² K. M. Al-Adil, E. R. White, W. L. Winterlin, and W. W. Kilgore, *J. Agr. Food Chem.* **21**, 376 (1973) [CA 79, 28143 (1973)].
- ²³³ R. D. O'Brien and A. N. Davidson, *Can. J. Biochem. Physiol.* **36**, 1203 (1958) [CA 53, 4583 (1959)]; I. Sato, *Kumamoto Med. J.* **12**, 312 (1959) [CA 54, 21473 (1960)].
- ²³⁴ H. Edery and G. Schatzberg-Porath, *Arch. Int. Pharmacodyn.* **121**, 104 (1959) [CA 54, 5924 (1960)].
- ²³⁵ S. D. Murphy and K. P. Dubois, *J. Pharmacol. Exp. Therap.* **119**, 572 (1957) [CA 51, 13956 (1957)]; D. F. McCalley and J. W. Cook, *J. Ass. Offic. Agr. Chem.* **42**, 200 (1959) [CA 53, 9498 (1959)]; R. D. O'Brien, *J. Agr. Food Chem.* **11**, 163 (1963) [CA 58, 11635 (1963)]; G. C. Guilbault, R. L. Lozes, W. Moore, and S. S. Kaun, *Environ. Lett.* **3**, 235 (1972) [CA 78, 53831 (1973)].
- ²³⁶ S. Gershon and F. H. Shaw, *Lancet*, 1371 (1961).
- ²³⁷ O. Wollenberg and G. Schrader, *Angew. Chem.* **68**, 41 (1956); J. J. Menn, W. R. Erwin, and H. T. Gordon, *J. Agr. Food Chem.* **5**, 601 (1957) [CA 51, 16989 (1957)]; I. Hornstein, *ibid.* **6**, 32 (1958) [CA 52, 7606 (1958)]; O. Wollenberg, *Angew. Chem.* **68**, 581 (1956); W. M. Hoskins, W. R. Erwin, R. Miskus, W. W. Thornburg, and L. N. Werum, *J. Agr. Food Chem.* **6**, 914 (1958); [CA 53, 16458 (1959)]; T. Shishido and M. Suwanai, *Nippon Nogei Kagaku Kaishi* **32**, 956 (1958) [CA 53, 15455 (1959)]; I. Kawashiro and H. Takeuchi, *Eisei Shikenjo Hikoku* **76**, 59 (1958) [CA 53, 17409 (1959)]; T. E. Archer and G. Zweig, *J. Agr. Food Chem.* **7**, 178 (1959) [CA 53, 19285 (1959)]; P. A. Giang and M. S. Schechter, *ibid.* **6**, 845 (1958) [CA 53, 15410 (1959)]; A. Matsunaga, A. Murakami, I. Sato, K. Yamashita, and H. Yoshimori, *Kumamoto Med. J.* **12**, 214 (1959) [CA 54, 11813 (1960)]; B. G. Hightower, *J. Econ. Entomol.* **52**, 840 (1959); H. F. MacRae and W. P. McKinley, *J. Ass. Offic. Agr. Chem.* **44**, 207 (1961) [CA 55, 20296 (1961)]; I. Sato, *Kumamoto Med. J.* **14**, 1 (1961) [CA 55, 24904 (1961)]; P. A. Dahm, J.

and of their hydrolysis and metabolic products,²³⁸ from foodstuffs²³⁹ and tobacco.^{230,240} Their long-term persistency has also been studied.²⁴¹ Antidotes to poisoning^{233,234} both in human^{225,227-229} and animal^{200,224,227,242} subjects have been investigated.

Application of compounds of the type 126 has been shown to result in increased crop yields under certain conditions,²⁴³ and they have been used as adjuvants for plants.²⁴⁴ The development of resistance and cross-resistance by insects has been studied.^{223,245}

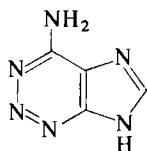
Many other simple esters of 3-hydroxymethyl-1,2,3-benzotriazin-4(3*H*)-one and the thiomethyl analog have been prepared and also found to possess insecticidal properties.^{222,246} 3-Trichloromethylthio-1,2,3-benzotriazin-4(3*H*)-one (10, R = SCl₃) has been shown to have nematocidal properties,¹⁵⁸⁻¹⁶¹ as do other 3-*S*-alkyl ethers,²⁴⁷ while the 3-

- Gurland, E. T. Hibbs, W. H. Orgell, W. O. Pfaelle, and I. Lee, *J. Econ. Entomol.* **52**, 791 (1959); L. C. Mitchell, *J. Ass. Offic. Agr. Chem.* **43**, 810 (1960) [*CA* **55**, 5845 (1961)]; M. C. Bowman and M. Beroza, *J. Ass. Offic. Anal. Chem.* **53**, 499 (1970) [*CA* **73**, 24179 (1970)]; R. L. Schutzmann and W. F. Barthel, *ibid.* **52**, 151 (1969) [*CA* **70**, 56345 (1969)]; R. S. Vickers, P. W. Chan, and R. E. Johnsen, *Spectrosc. Lett.* **6**, 131 (1973); G. L. Brun and V. Mallet, *J. Chromatogr.* **80**, 117 (1973).
- ²³⁸ R. Muhlmann and G. Schrader, *Z. Naturforsch. B* **12**, 196 (1957). D. Katz and I. Lempert, *J. Chromatogr.* **14**, 133 (1964); K. R. Schulz, E. P. Lichtenstein, T. T. Liang, and T. W. Fuhremann, *J. Econ. Entomol.* **63**, 432 (1970).
- ²³⁹ *Fed. Regist.* **24**, 4830 (1959) [*CA* **53**, 17360 (1959)]; Anonymous, *J. Ass. Offic. Agr. Chem.* **44**, 133 (1961) [*CA* **55**, 14155 (1961)]; W. S. Cox, *ibid.* **44**, 188 (1961) [*CA* **55**, 26291 (1961)]; W. R. Meagher, J. M. Adams, C. A. Anderson, and D. MacDougall, *J. Agr. Food Chem.* **8**, 282 (1960) [*CA* **55**, 22638 (1961)]; E. Q. Laws and D. J. Webley, *Analyst* **86**, 249 (1961); J. R. W. Miles, *J. Ass. Offic. Agr. Chem.* **47**, 882 (1964) [*CA* **61**, 15258 (1962)]; D. A. Wolfenbarger and T. N. Shaver, *J. Econ. Entomol.* **66**, 332 (1973).
- ²⁴⁰ T. G. Bowery and F. E. Guthrie, *J. Agr. Food Chem.* **9**, 193 (1961) [*CA* **55**, 21453 (1961)].
- ²⁴¹ *Fed. Regist.* **25**, 8321 (1960) [*CA* **54**, 25363 (1960)]; M. R. Osburn, L. H. Dawsey, and D. W. Woodham, *J. Econ. Entomol.* **53**, 719 (1960); B. G. Hightower and D. F. Martin, *ibid.* **51**, 669 (1958); H. E. Dorst, *ibid.* **52**, 172 (1959).
- ²⁴² A. Maher Ali, M. S. Sawy, R. H. Bishara, M. M. A. Kader, and M. Husein, *Agr. Res. Rev.* **36**, 159 (1958) [*CA* **53**, 13491 (1959)]; L. D. Anderson and F. L. Atkins, *J. Econ. Entomol.* **51**, 103 (1958); R. D. Radeleff and G. T. Woodard, *J. Amer. Vet. Med. Ass.* **130**, 215 (1957) [*CA* **51**, 10823 (1957)].
- ²⁴³ D. S. Rao, *Curr. Sci.* **29**, 480 (1960) [*CA* **55**, 11745 (1961)].
- ²⁴⁴ F. R. Horsfall and R. C. Moore, *Proc. Amer. Soc. Hort. Sci.* **77**, 9 (1961) [*CA* **55**, 25137 (1961)].
- ²⁴⁵ J. B. Graves, J. S. Roussel, J. Gibbens, and D. Patton, *J. Econ. Entomol.* **60**, 47 (1967); J. Hurkova, *Acta Entomol. Bohemoslov.* **70**, 13 (1973) [*CA* **79**, 74902 (1973)]; F. A. M. Mariconi, N. T. Murai, M. Yoshizaki, and T. Idagawa, *Biologico* **38**, 416 (1972) [*CA* **79**, 49784 (1973)]; V. Koellner, *Nachrichtenbl. Deut. Pflanzenschutzdiensies (Brunswick)* **25**, 7 (1973) [*CA* **79**, 28360 (1973)].
- ²⁴⁶ Japanese Patent 1791 (1966) [*CA* **64**, 12740 (1966)]; U.S. Patent 3,532,697 [*CA* **74**, 100109 (1971)].
- ²⁴⁷ Ger. Offen. 2,065,047 [*CA* **76**, 140900 (1972)]; U.S. Patent 3,652,560 [*CA* **76**, 153792 (1972)].

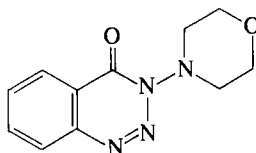
cyanatomethyl derivative is fungicidal.²⁴⁸ Other benzotriazinone derivatives reported to have insecticidal properties include the 3-hydroxy compound (40),^{83,249} some halo N-oxides,^{45,250} and certain compounds bearing multifunctional alkyl groups at N₃.²⁵¹

2. Pharmaceuticals

Considerable interest has developed during the last ten years in the potential utility of condensed 1,2,3-triazine derivatives as medicinals, although the first indication that these compounds might be useful appears to be the report by Woolley and Shaw in 1951 that the "2-azadenine" derivative (183) inhibited hypoxanthine activity in *Lactobacillus brevis*.^{78,98} 1,2,3-Benzotriazin-4-one (10, R = H) is reported



(183)



(184)

to induce a weak sedative effect; and the 3-amino derivative, a pronounced hypnotic effect coupled with a strong emetic action.²⁵² A wide variety of 3-alkylamino and 3-dialkylamino derivatives of 10, R = H, have since been prepared,^{252,253} and the 3-morpholino compound (184) was found to be among the most useful; it has an analgesic activity superior to that of phenacetin and aminopyrine, but a lower acute toxicity.²⁵⁴ Variation in the nature of the alkyl groups in the 3-alkylamino and 3-dialkylamino derivatives has been shown to result in considerable variation in pharmacological activity, but introduction of substituents into the benzene ring generally results in only minor changes. The types of activity shown by these compounds varies from weakly analgesic to prolonged hypnotic, narcotic, muscle relaxant, diuretic and strongly analgesic (for a complete classification see Petersen *et al.*²⁵²).

The hydroxycarbamate derivative 185 is a powerful muscle relaxant which has been recommended for use in cases of severe tension and for

²⁴⁸ U.S. Patent 2,949,465 [CA 55, 7448 (1961)].

²⁴⁹ H. H. S. Bovington, *Ann. Appl. Biol.* **46**, 47 (1958) [CA 52, 12306 (1958)].

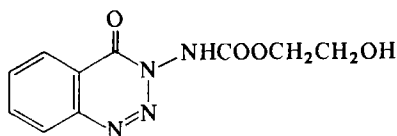
²⁵⁰ French Patent 1,373,006 [CA 62, 9154 (1965)].

²⁵¹ Netherlands Appl. 6,503,900 [CA 64, 8239 (1966)].

²⁵² S. Peterson, H. Herlinger, E. Tietze, and W. Siefken, *Angew. Chem., Int. Ed. Engl.* **2**, 24 (1963).

²⁵³ Ger. Offen. 1,121,055 [CA 56, 15523 (1962)].

²⁵⁴ French Patent M2341 [CA 61, 8141 (1964)].



(185)

some mental illnesses,²⁵⁵ and the water-soluble sodium salts of related carbamates have been found to be superior in practice.²⁵⁶ Several other 3-dialkylamino and 3-acylamino derivatives have been reported to show sedative and hypnotic properties and have been patented.²⁵⁷ It has been claimed that a series of 3-alkyl-, 3-alkylamino-, and 3-imino-alkyl derivatives of 6-sulfamoyl-7-chloro-1,2,3-benzotriazin-4(3*H*)-one show diuretic activity,²⁵⁸ while the 3-dialkylaminomethyl compounds function as antidepressants.²⁵⁹ Some nuclear halogenated 3-alkyl derivatives are useful sedatives for the treatment of psychoneurosis,²⁶⁰ and related compounds have been stated to have antiphlogistic, antipyretic, and sedative activity.²⁶¹

A series of esters of nuclear halogenated 3-carboxy-1,2,3-benzotriazin-4(3*H*)-ones show depressant activity, while the benzoate esters of substituted 3-(2-hydroxyethyl)-1,2,3-benzotriazin-4(3*H*)-one are reported to function as coronary dilating agents,²⁶² as do certain other compounds of this type.²⁶³ 3-(*o*-Haloaryl)-1,2,3-benzotriazin-4(3*H*)-ones are claimed to have antisecretory,²⁶⁴ anorectic, anticonvulsant, and hypoglycemic²⁶⁵ activity, and a variety of other 3-aryl derivatives are stated to be relaxants, tranquilizers, sedatives, hypnotics, or cramp inhibitors.²⁶⁶ A number of derivatives of 10, R = H, in which the 3-substituent is a long alkyl chain containing a terminal sulfonamide group have been claimed to act as antidiabetics.²⁶⁷

²⁵⁵ Belgian Patent 612,389 [CA 57, 16638 (1962)]; British Patent 932,680 [CA 60, 4162 (1964)]; F. Hoffmeister, *Arch. Int. Pharmacodyn.* 148, 382 (1964) [CA 61, 2352 (1964)].

²⁵⁶ British Patent 896,846 [CA 57, 12516 (1962)]; U.S. Patent 3,075,982 [CA 59, 2837 (1963)].

²⁵⁷ Belgian Patent 630,848 [CA 61, 9512 (1964)].

²⁵⁸ U.S. Patent 3,014,906 [CA 56, 10171 (1962)]; S. M. Gadekar and J. L. Frederick, *J. Org. Chem.* 27, 1383 (1962); Swiss Patent 405,332 [CA 65, 15402 (1966)].

²⁵⁹ Netherlands Appl. 6,702,189 [CA 70, 57912 (1969)].

²⁶⁰ Netherlands Appl. 6,603,319 [CA 68, 114665 (1968)].

²⁶¹ Ger. Offen. 1,223,846 [CA 65, 18602 (1966)].

²⁶² French Patent 2,051,552 [CA 76, 99715 (1972)].

²⁶³ Ger. Offen. 1,926,076 [CA 74, 53859 (1971)]; Ger. Offen. 1,926,075 [CA 74, 42391 (1971)].

²⁶⁴ Ger. Offen. 2,012,094 [CA 76, 3908 (1972)]; Ger. Offen 2,065,047 [CA 76, 140900 (1972)].

²⁶⁵ Ger. Offen. 1,271,118 [CA 69, 77283 (1968)].

²⁶⁶ Ger. Offen. 2,061,474 [CA 77, 114436 (1972)]; Ger. Offen. 1,249,876 [CA 68, 21966 (1968)].

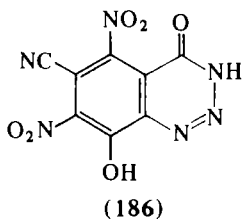
²⁶⁷ Ger. Offen. 2,103,118 [CA 77, 140159 (1972)].

3. Dyestuffs

As mentioned previously (see p. 237), the 1,2,3-benzotriazinones function as "masked" diazonium compounds, and the so-called "Pologenowe" dyes developed in Poland are operated on this principle and have been in use there since 1959. There are three major advantages associated with the use of 1,2,3-benzotriazinones as azo-dye equivalents: (1) The equilibrium that theoretically exists between the heterocyclic system and the diazonium compound normally lies completely to the side of the cyclic compound. Opening of the heterocyclic ring can be easily accomplished thermally, and hence dye formation can be induced by heat treatment processes.²⁶⁸ (2) Many 1,2,3-benzotriazinones are reasonably water soluble and the sodium salts even more so; consequently, complete permeation of fabric fibres by the dye precursors immediately prior to generation of the dye can be ensured.²⁶⁹ (3) The colors produced are "fast,"²⁷⁰ and some of them can be made highly water insoluble.²⁷¹

4. Miscellaneous

The highly substituted derivative **186**, in the form of the potassium salt, has been recommended for use in detonators in place of the more dangerous mercury fulminate.²⁷² 1,2,3-Benzotriazine-4-thione (**39**, R = H) has been used in photographic transfer emulsions as an inhibitor and toning agent,²⁷³ and heavy metal salts of the oxygen analog **10**, R = H are employed as photodevelopable emulsions.²⁷⁴ The latter compound is also claimed to be useful as a stabilizer in olefin polymers²⁷⁵ and as an antioxidant in certain other polymers.²⁷⁶ Dimeric derivatives of **10** have



²⁶⁸ J. Zychowicz, *Chemik* **16**, 277 (1963) [*CA* **60**, 10827 (1964)].

²⁶⁹ W. Kullick, *Angew. Chem., Int. Ed. Engl.* **5**, 675 (1966).

²⁷⁰ Polish Patent 46,243 [*CA* **60**, 5669 (1964)].

²⁷¹ Ger. Offen. 1,101,658 [*CA* **55**, 24026 (1961)].

²⁷² Ger. Offen. 1,189,425 [*CA* **62**, 15986 (1965)].

²⁷³ British Patent 975,243 [*CA* **62**, 1247 (1965)].

²⁷⁴ U.S. Patent 3,652,287 [*CA* **77**, 27403 (1972)].

²⁷⁵ Netherlands Appl. 6,500,129 [*CA* **63**, 18379 (1965)].

²⁷⁶ R. H. Hansen, T. De Benedictis, and W. M. Martin, *Polymer Eng. Sci.* **5**, 223 (1965) [*CA* **64**, 5255 (1966)]; U.S. Patent 3,367,907 [*CA* **68**, 69766 (1968)].

been used as foaming agents in both nylon and propylene polymers²⁷⁷ and as blowing agents for thermoplastics.^{278,279} Both **10**, R = H,²⁸⁰⁻²⁸² in the presence of diimides, and the 3-hydroxy derivative **40** have been used in peptide synthesis.^{280,281,283,284} Interestingly, **10**, R = H, has been found to show contraceptive activity in both male and female mice, but this observation has not apparently been followed further.²⁸⁵

A number of 2-alkyl-1,2,3-benzotriazinium salts similar to those described earlier have been used in protective coatings²⁸⁶ and in the formulation of adhesives.²⁸⁷ 3-Alkyl-1,2,3-benzotriazin-4(3*H*)-ones have been examined as potential irreversible inhibitors of chymotrypsin,¹⁸⁹ and the 3-(1-adamantyl) derivative as a potential virus inhibitor.²⁸⁸ Some unspecified 1,2,3-benzotriazine derivatives have been tested as radioprotectant compounds (to complement the well-known mercaptoethylamine and mercaptoalkylisothiuronium compounds), but were found to be ineffective.²⁸⁹

²⁷⁷ Ger. Offen. 2,054,494 [CA 75, 50029 (1971)].

²⁷⁸ Ger. Offen. 2,103,198 [CA 77, 153420 (1972)].

²⁷⁹ Ger. Offen. 2,126,145 [CA 78, 59289 (1973)].

²⁸⁰ W. König and R. Geiger, *Chem. Ber.* **103**, 2024 (1970).

²⁸¹ W. König and R. Geiger, *Chem. Ber.* **103**, 2034 (1970).

²⁸² Ger. Offen. 2,202,613 [CA 79, 137510 (1973)].

²⁸³ Ger. Offen. 1,939,187 [CA 75, 36699 (1971)].

²⁸⁴ E. Heidermann and H.-D. Meisel, *Makromol. Chem.* **166**, 1 (1973).

²⁸⁵ W. C. Cutting, J. Rogers, J. Roberts, and P. Tabar, *Med. Pharmacol. Exp.* **15**, 7 (1966) [CA 65, 4489 (1966)].

²⁸⁶ Japanese Patent 71 07,606 [CA 76, 61182 (1972)].

²⁸⁷ U.S. Patent 3,681,168 [CA 77, 115642 (1972)].

²⁸⁸ A. Kreutzberger and H. H. Schroeders, *Tetrahedron Lett.*, 4523 (1970).

²⁸⁹ T. J. Haley, A. M. Flesher, and L. Mavis, *Arch. Int. Pharmacodyn.* **138**, 133 (1962) [CA 57, 15461 (1962)].

Synthesis of Heterocycles through Nucleophilic Additions to Acetylenic Esters

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I. Introduction

Numerous reactions of acetylenic esters are reported in the literature, and many of these lead to heterocyclic compounds. Acetylenic esters undergo very facile addition reactions with several nucleophiles and also they participate as dipolarophiles in 1,3-dipolar cycloadditions, and as

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dienophiles in Diels–Alder additions. Several reviews have appeared highlighting various aspects of the chemistry of acetylenic esters.^{1–9}

The present review is intended to highlight the use of acetylenic esters in the synthesis of different heterocycles, primarily involving nucleophilic additions. The reactions of heterocyclic bases with acetylenic esters, however, will not be covered here, except in a few cases where it is more appropriate for inclusion here, depending on the type of reactions. The reactions of heterocyclic bases form the subject matter of a separate article.^{3b} The survey covers the literature up to December 1973.

II. Nitrogen-Containing Nucleophiles

A. PRIMARY AMINES

The reaction of amines with acetylenic esters has been investigated in detail by several groups of workers.¹⁰ In general, primary amines react

¹ A. W. Johnson, "The Chemistry of the Acetylenic Compounds," Vol. 2. Arnold, London, 1950.

² R. A. Raphael, "Acetylenic Compounds in Organic Synthesis." Academic Press, New York, 1955.

³ (a) R. M. Acheson, *Advan. Heterocycl. Chem.* **1**, 125 (1963); (b) R. M. Acheson, private communication.

⁴ (a) R. Huisgen, *Angew. Chem.* **75**, 741 (1963); *Angew. Chem., Int. Ed. Engl.* **2**, 633 (1963); (b) R. Huisgen, R. Grashey, and J. Sauer, in "Chemistry of Alkenes" (S. Patai, ed.), Chapter 11. Wiley (Interscience), New York, 1964; (c) R. Huisgen, *Bull. Soc. Chim. Fr.*, 3431 (1965) [*CA* **64**, 7987 (1966)].

⁵ E. Winterfeldt, *Angew. Chem., Int. Ed. Engl.* **6**, 423 (1967).

⁶ R. Fuks and H. G. Viehe, in "Chemistry of Acetylenes" (H. G. Viehe, ed.), Chapter 8. Dekker, New York, 1969.

⁷ T. F. Rutledge, "Acetylenes and Allenes, Addition, Cyclization and Polymerization." Reinhold, New York, 1969.

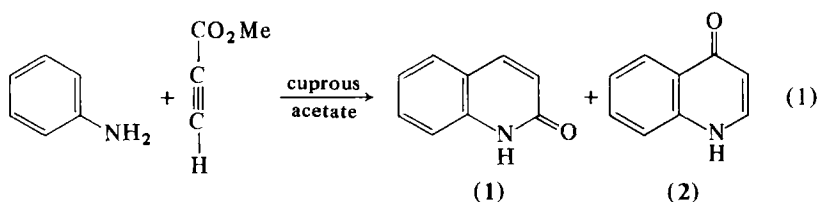
⁸ S. I. Miller and R. Tanaka, in "Selective Organic Transformations" (B. S. Thyagrajan, ed.), Vol. 1, Chapter 4. Wiley (Interscience), New York, 1970.

⁹ V. M. Baumgarth, *Chem. Ztg.* **96**, 361 (1972).

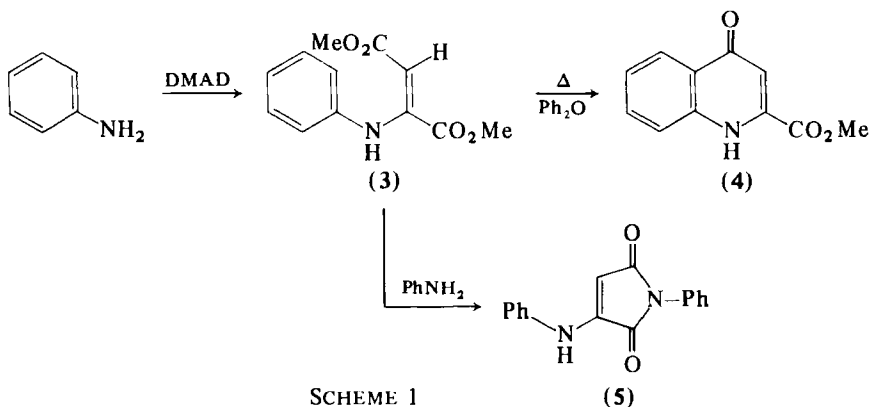
¹⁰ For some of the reactions of primary amines with acetylenic esters, see: (a) E. Buchner, *Ber.* **22**, 2929 (1889); (b) C. Moureu and I. Lazennec, *C. R. Acad. Sci.* **143**, 596 (1906); *Bull. Soc. Chim. Fr.* **35**, 1190 (1906) [*CA* **1**, 731 (1907)]; (c) F. W. Gray, H. S. Mosher, F. C. Whitmore, and T. S. Oakwood, *J. Amer. Chem. Soc.* **73**, 3577 (1951); (d) Y. Iwanami, *Nippon Kagaku Zasshi* **82**, 632, 634 (1961) [*CA* **56**, 10007 (1962)]; (e) Y. Iwanami, *Nippon Kagaku Zasshi* **83**, 590 (1962) [*CA* **59**, 3919 (1963)]; (f) R. Huisgen, K. Herbig, A. Siegl, and H. Huber, *Chem. Ber.* **99**, 2526 (1966); (g) K. Herbig, R. Huisgen, and H. Huber, *ibid.* **99**, 2546 (1966); (h) W. Bottomley, *Tetrahedron Lett.*, 1997 (1967); (i) S. Toppet, E. V. Looock, G. L'abbé, and G. Smets, *Chem. Ind. (London)*, 703 (1971); (j) N. D. Harris, *Synthesis* **48** (1973); (k) M. Neuenschwander and P. Bigler, *Helv. Chim. Acta* **56**, 959 (1973); (l) A. Niederhauser, A. Frey, and M. Neuenschwander, *ibid.* **56**, 944 (1973).

with dimethyl acetylenedicarboxylate (DMAD), giving rise chiefly to the enamine fumarates. The preferential formation of the fumarates in these additions can be understood in terms of their relative stabilities, as compared to the corresponding maleates, due to internal hydrogen bonding.^{10c,f,i,j} Several factors affecting the stereochemistry of this type of addition have also been studied in detail.^{10f,s}

The enamine adducts formed in the reaction of aromatic amines with DMAD have been found to undergo cyclization leading to heterocyclic compounds, and the mode of these reactions is to a considerable extent influenced by the reaction conditions, the catalyst employed, and also the nature of the functional groups present in the starting amine. The reaction of aniline with methyl propiolate in presence of cuprous acetate, for example, is reported to give a mixture of 2(1*H*)-quinolone (1) and 4(1*H*)-quinolone (2) [Eq. (1)].¹¹ On the other hand, dimethyl anilinfumarate (3), formed from aniline with DMAD, undergoes



cyclization to 2-carbomethoxy-4(1*H*)-quinolone (4), in refluxing diphenyl ether.^{10f,12} The reaction of excess aniline with DMAD,

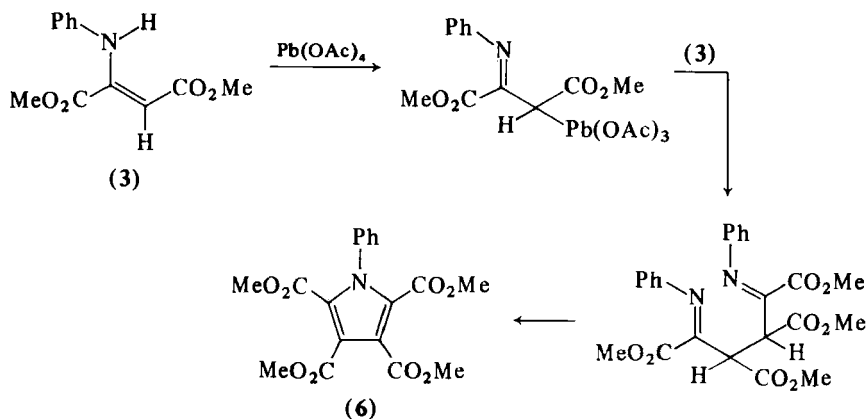


SCHEME 1

¹¹ J. Reisch, *Angew. Chem.* **75**, 1203 (1963); *Angew. Chem., Int. Ed. Engl.* **2**, 741 (1963).

¹² S. K. Khetan, J. G. Hiriyakkanavar, and M. V. George, *Tetrahedron* **24**, 1567 (1968).

however, yields α -anilino-*N*-phenylmaleimide (5). The same product (5) is obtained on direct heating of (3) with aniline (Scheme 1).¹³ An interesting mode of cyclization of dimethyl anilino fumarate (3) involves the formation of tetracarbomethoxy-*N*-phenylpyrrole (6), on treatment with lead tetraacetate (Scheme 2).¹⁴



SCHEME 2

The reaction of *ortho*-substituted anilines containing substituent groups, e.g., phenyl,¹⁵ cyano,¹⁶ and nitro,¹⁷ gives rise to simple enamine fumarates; these in turn can be cyclized to the corresponding 4-quinolones.¹⁵⁻¹⁷ Aromatic diamines such as *o*-phenylenediamine and 2,3-diaminonaphthalene, however, react with DMAD to give tetrahydroquinoxaline derivatives (7) [Eq. (2)].^{10a,18-20} It has been suggested that these tetrahydroquinoxalines exist in tautomeric equilibrium between the imine and enamine forms²¹ and that the enamine form (7) is more favored in inert organic solvents.²² On the other hand, an iso-

¹³ N. D. Heindel, *J. Org. Chem.* **35**, 3138 (1970).

¹⁴ S. K. Khetan, *Chem. Commun.*, 917 (1972).

¹⁵ K. Nagarajan, M. D. Nair, R. K. Shah, and J. A. Desai, *Indian J. Chem.* **11**, 112 (1973).

¹⁶ N. D. Heindel, T. A. Brodof, and J. E. Kogelschatz, *J. Heterocycl. Chem.* **3**, 222 (1966).

¹⁷ N. D. Heindel, I. S. Bechara, T. F. Lemke, and V. B. Fish, *J. Org. Chem.* **32**, 4155 (1967).

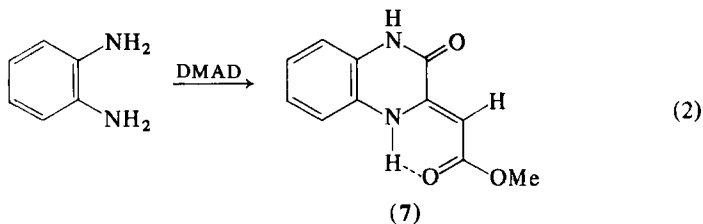
¹⁸ N. D. Heindel, T. F. Lemke, H. R. Harless, and L. E. Brydia, *Proc. West Va. Acad. Sci.* **38**, 250 (1966) [*CA* **68**, 59552 (1967)].

¹⁹ Y. Iwanami, *Nippon Kagaku Zasshi* **82**, 778 (1961) [*CA* **58**, 11354 (1963)].

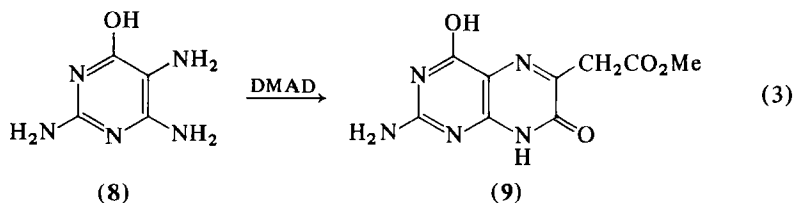
²⁰ Y. Iwanami, *Nippon Kagaku Zasshi* **83**, 316 (1962) [*CA* **59**, 3919 (1963)].

²¹ D. D. Chapman, *J. Chem. Soc., C* 806 (1966).

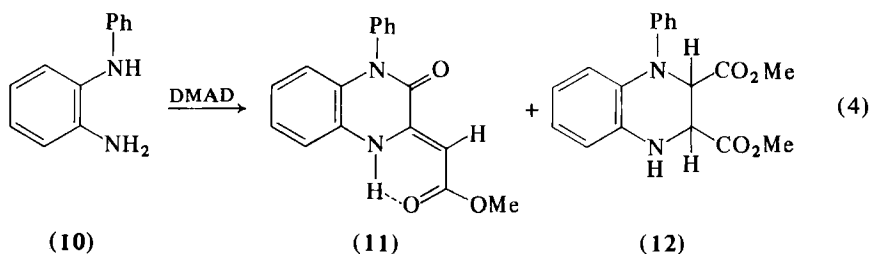
²² Y. Iwanami, *Bull. Chem. Soc. Jap.* **44**, 1311 (1971) [*CA* **75**, 48007 (1971)].



xanthopterin derivative (9) formed from 2,5,6-triamino-4-hydroxypyrimidine (8) with DMAD, exists chiefly in the imine form [Eq. (3)].²³



The reaction of *N*-phenyl-*o*-phenylenediamine (10) with DMAD gives a mixture of products consisting of 1-phenyl-2-oxo-3-carbomethoxymethylene-1,2,3,4-tetrahydroquinoxaline (11) and 1-phenyl-2,3-dicarbo-methoxy-1,2,3,4-tetrahydroquinoxaline (12) [Eq. (4)].²⁴ *m*-Phenylenediamine and *p*-phenylenediamine give the corresponding bisenamines 13



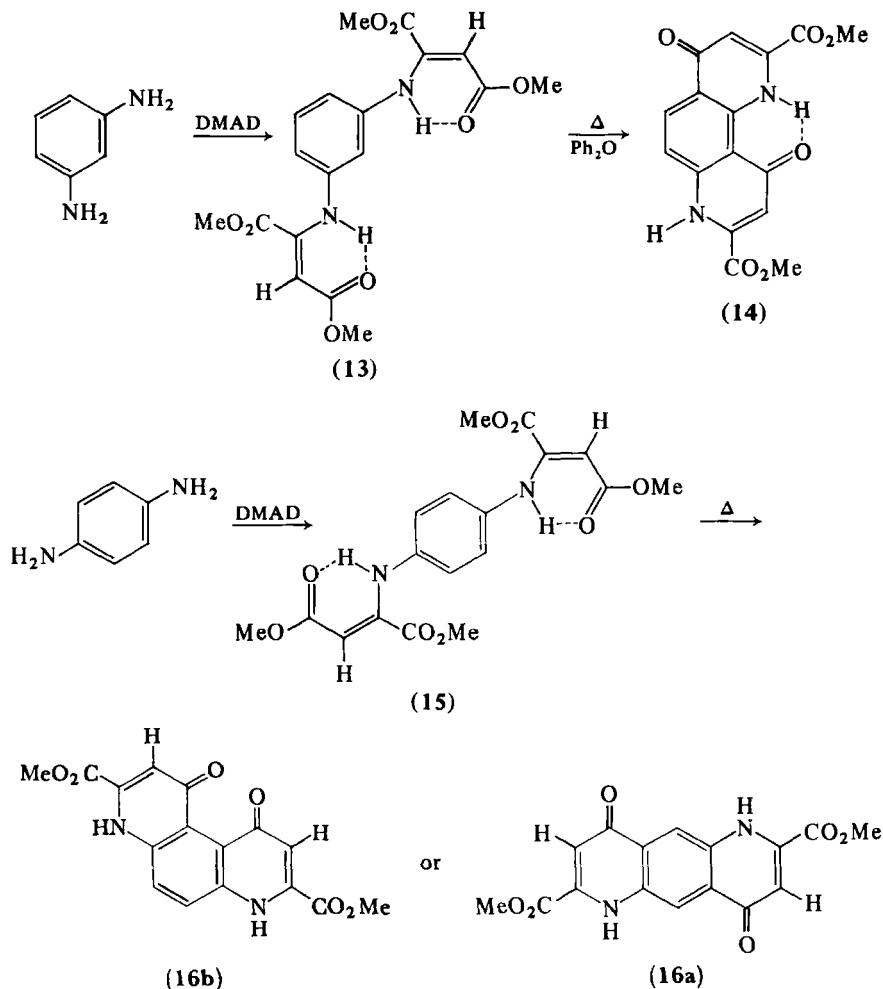
and 15, which on subsequent cyclization yield the quinolone derivatives 14 and 16,^{25a} respectively (Scheme 3).^{25b} Similarly, the reaction of 2,2'-diaminobiphenyl gives a bisenamine adduct, which is subsequently cyclized to a bisquinolone system on refluxing in diphenyl ether.^{25a} A

²³ Y. Iwanami, *Bull. Chem. Soc. Jap.* **44**, 1314 (1971) [*CA* **75**, 47994 (1971)].

²⁴ M. D. Nair and S. R. Mehta, *Indian J. Chem.* **6**, 490 (1968).

²⁵ (a) S. K. Khetan and M. V. George, *Can. J. Chem.* **47**, 3545 (1969).

²⁵ (b) An alternative to 16a is its angularly formed isomer 16b, which is not excluded by the evidence of Khetan and George.^{25a}

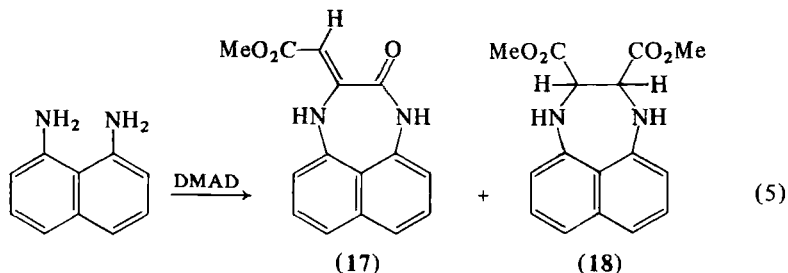


SCHEME 3

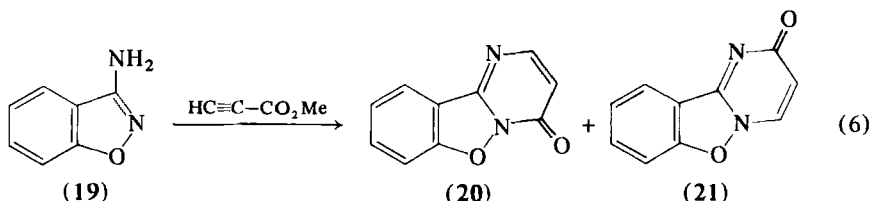
mixture of azepines 17 and 18 has been obtained in the reaction of 1,8-diaminonaphthalene with DMAD [Eq. (5)].²⁶ In the reaction of an aliphatic amine, such as ethylenediamine with DMAD, a piperazine derivative is formed.²⁷ Reactions of several amino heterocycles, such as 1-aminoisoquinoline, 3-aminopyrazole, 3-amino-1,2,4-triazole, 3-aminobenzisoxazole, 3-aminoindazole, 3-amino-4,5,6,7-tetrahydroindazole, and 2-amino-*s*-triazolo[1,5-*a*]pyridine with propiolic esters have been

²⁶ Y. Iwanami, *Nippon Kagaku Zasshi* **83**, 597 (1962) [CA **59**, 3920 (1963)].

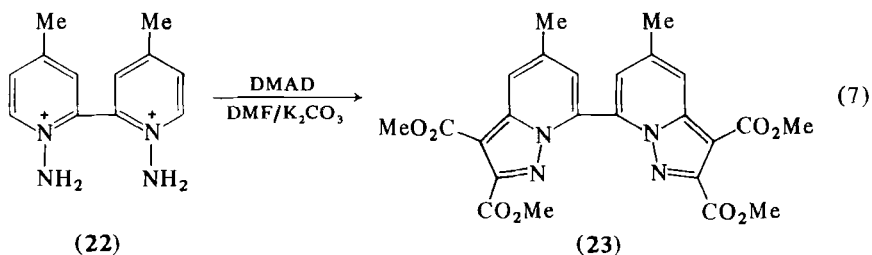
²⁷ Y. Iwanami, Y. Kenjo, K. Nishibe, M. Kajiura, and S. Isayama, *Bull. Chem. Soc. Jap.* **37**, 1740 (1964) [CA **62**, 7755 (1964)].



shown to give condensed pyrimidones.²⁸⁻³⁴ Thus, in the reaction of 3-aminobenzisoxazole (19) with methyl propiolate, the isomeric oxopyrimido[1,2-*b*]benzisoxazoles 20 and 21 are formed [Eq. (6)].³¹ In the



reaction of 5-aminotetrazole with methyl propiolate, on the other hand, a mixture of simple 1:1 and 1:2 adducts having the fumarate geometry is formed.³⁴ Tamura *et al.*³⁵ have recently shown that *N,N'*-diamino-2,2'- and 4,4'-bipyridinium salts react with DMAD to give the corresponding bispyrazolo[1,5-*a*]pyridine derivatives.³⁵ Thus, 7,7'-bipyrazolo[1,5-*a*]pyridine (23) is formed in the reaction of *N,N'*-diamino-4,4'-dimethyl-2,2'-bipyridinium dimesitylenesulfonate (22) in the presence of potassium carbonate [Eq. (7)].



²⁸ H. Reimlinger, F. Billiau, M. A. Peiren, and R. Merenyi, *Chem. Ber.* **105**, 108 (1972).

²⁹ H. Reimlinger, M. A. Peiren, and R. Merenyi, *Chem. Ber.* **103**, 3252 (1970).

³⁰ H. Reimlinger, R. Jacquier, and J. Daunis, *Chem. Ber.* **104**, 2702 (1971).

³¹ H. Reimlinger, M. A. Peiren, and R. Merenyi, *Chem. Ber.* **105**, 794 (1972).

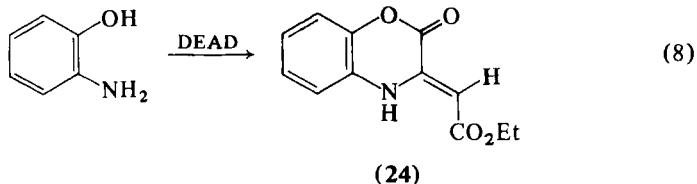
³² D. W. Dunwell and D. Evans, *J. Chem. Soc. Perkin Trans. I* 1588 (1973).

³³ S. Plescia, V. Spiro, and M. L. Marino, *J. Heterocycl. Chem.* **10**, 261 (1973).

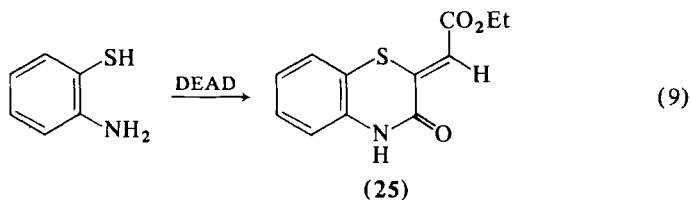
³⁴ H. Reimlinger, M. A. Peiren, and R. Merenyi, *Chem. Ber.* **105**, 103 (1972).

³⁵ Y. Tamura, Y. Miki, and M. Igeda, *J. Heterocycl. Chem.* **10**, 447 (1973).

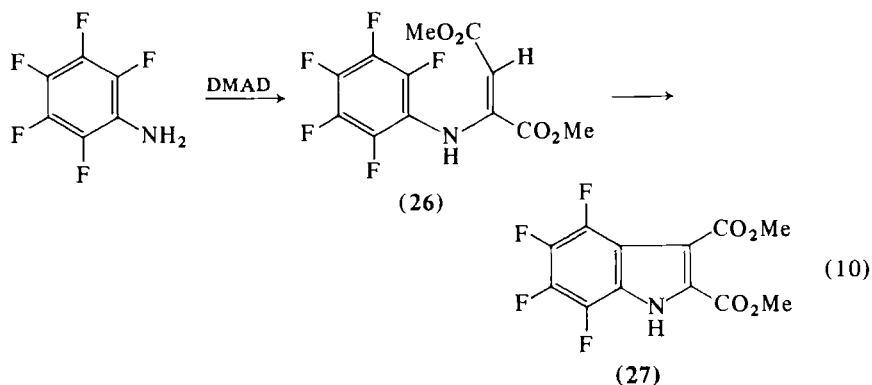
Several substituted hydroxy amines have been treated with acetylenic esters to give different heterocyclic systems.^{36,37} Thus, the reaction of *o*-aminophenol with diethyl acetylenedicarboxylate gives 3-carbethoxymethylene-3,4-dihydro-2*H*-1,4-benzoxazin-2-one (24) [Eq. (8)].³⁶ In



contrast, the reaction of *o*-aminothiophenol leads to the formation of 2-carbethoxymethylene-3,4-dihydro-3-oxo-2*H*-benzo-1,4-thiazine (25) [Eq. (9)].^{38,39} An analogous reaction of ethanolamine with diethyl acetylenedicarboxylate gives a 1,4-oxazin-2-one derivative.³⁶



Brooke and Rutherford⁴⁰ have observed that pentafluoroaniline reacts with DMAD to give an enamine fumarate (26), which in presence of a strong base is cyclized through a nucleophilic displacement of a fluoride ion to give dimethyl 4,5,6,7-tetrafluoroindole-2,3-dicarboxylate (27) [Eq. (10)].



³⁶ Y. Iwanami, *Nippon Kagaku Zasshi* **82**, 780 (1961) [CA **58**, 11354 (1963)].

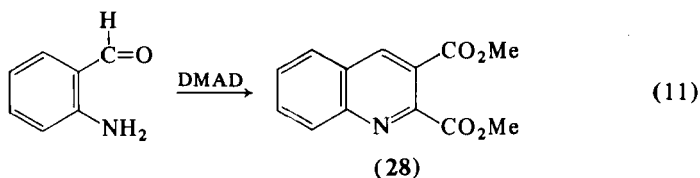
³⁷ Y. Iwanami, S. Isoyama, and Y. Kenjo, *Bull. Chem. Soc. Jap.* **37**, 1745 (1964).

³⁸ S. M. Kalbag, M. D. Nair, P. Rajagopalan, and C. N. Talaty, *Tetrahedron* **23**, 1911 (1967).

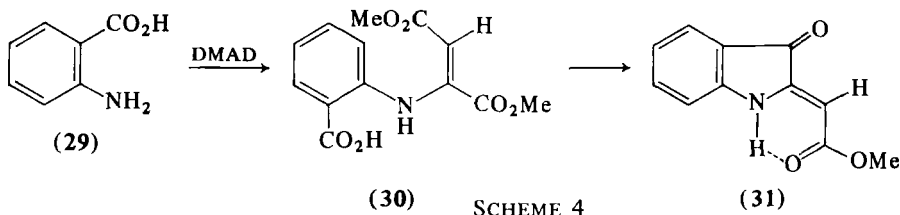
³⁹ Y. Maki and M. Suzuki, *Chem. Pharm. Bull.* **20**, 832 (1972) [CA **77**, 61922 (1972)].

⁴⁰ G. M. Brooke and R. J. D. Rutherford, *J. Chem. Soc., C*, 1189 (1967).

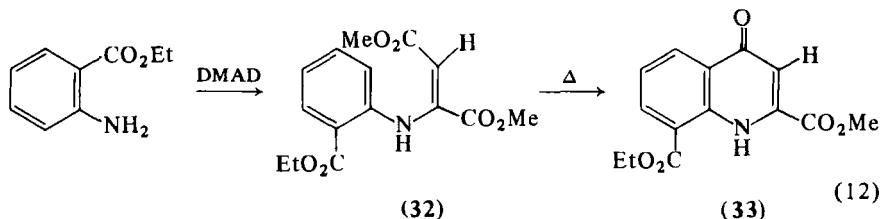
The reaction of *o*-aminobenzaldehyde with DMAD gives rise to dimethyl quinoline-2,3-dicarboxylate (28) [Eq. (11)].⁴¹ Similarly, the



reaction of 6-aminopiperonal gives an analogous quinoline derivative.^{42,43} The reaction of anthranilic acid (29) with DMAD is of interest in that the initially formed enamine fumarate (30) on refluxing in diphenyl ether forms an intermediate (*m/e* 247) of unknown structure, which, on further heating in the absence of solvent gives methyl 3-oxo-indolinyldeneacetate (31) (Scheme 4).^{25a} The reaction of ethyl



anthranilate, on the other hand, gives rise to the enamine fumarate 32, which can be thermally cyclized to 8-carbethoxy-2-carbomethoxy-4(1*H*)-quinolone (33)¹² [Eq. (12)]. Similar quinolone derivatives have



been obtained in the reaction of isatoic anhydride with DMAD in basic medium, and it has been suggested that the initial reaction involves the formation of anthranilic ester.⁴⁴

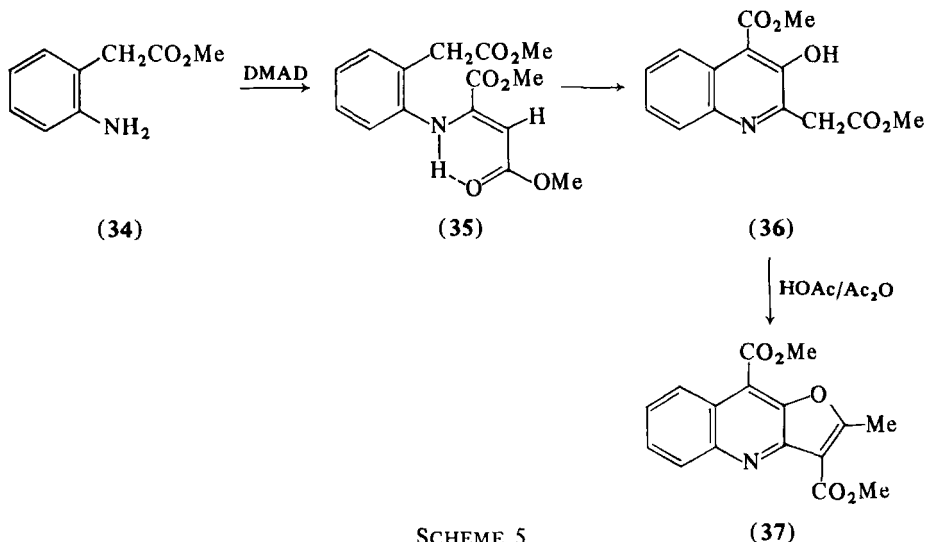
⁴¹ J. Reisch, *Pharmazie* 26, 420 (1967) [*CA* 68, 78099 (1968)].

⁴² J. B. Hendrickson and R. Rees, *J. Amer. Chem. Soc.* 83, 1250 (1961).

⁴³ J. B. Hendrickson, R. Rees, and J. F. Templeton, *J. Amer. Chem. Soc.* 86, 107 (1964).

⁴⁴ E. C. Taylor and N. D. Heindel, *J. Org. Chem.* 32, 3339 (1967).

Winterfeldt and Nelke⁴⁵ have observed the formation of the enamine derivative **35** in the reaction of methyl *o*-aminophenylacetate (**34**) with DMAD, which is subsequently cyclized to 3-hydroxy-2-carbomethoxymethyl-4-carbomethoxyquinoline (**36**), in the presence of sodium methoxide. Acylation of the quinoline derivative (**36**) leads to a furoquinoline (**37**) (Scheme 5).⁴⁶



SCHEME 5

The reaction of anthranilamide (**38a**) with DMAD gives the expected enamine fumarate (**39**), which undergoes different modes of cyclization depending upon the reaction conditions.⁴⁷⁻⁴⁹ Thus, treatment of **39** with sodium methoxide in xylene gives 2-carbomethoxymethylene-1,4-benzodiazepine-3,5-(1*H*,4*H*)-dione (**40**), whereas in methanolic sodium methoxide, 2-carbomethoxy-2-carbomethoxymethyl-2,3-dihydro-4(1*H*)-quinazolinone (**41**) is formed (Scheme 6). A similar mode of addition has been observed in the cases of anthranilohydroxamic acid, benzyl *o*-aminobenzohydroxamate and anthranilophenylhydrazide, yielding 2,3-dihydro-4(1*H*)-quinazolinones.⁵⁰ Recently, Nair⁵¹ has observed that in the reaction of anthranil hydrazide (**38b**) with DMAD, an enaminic ester (**42**) is formed, which on acylation yields the triazepine derivative

⁴⁵ E. Winterfeldt and J. M. Nelke, *Chem. Ber.* **103**, 1183 (1970).

⁴⁶ E. Winterfeldt, *Chem. Ber.* **104**, 677 (1971).

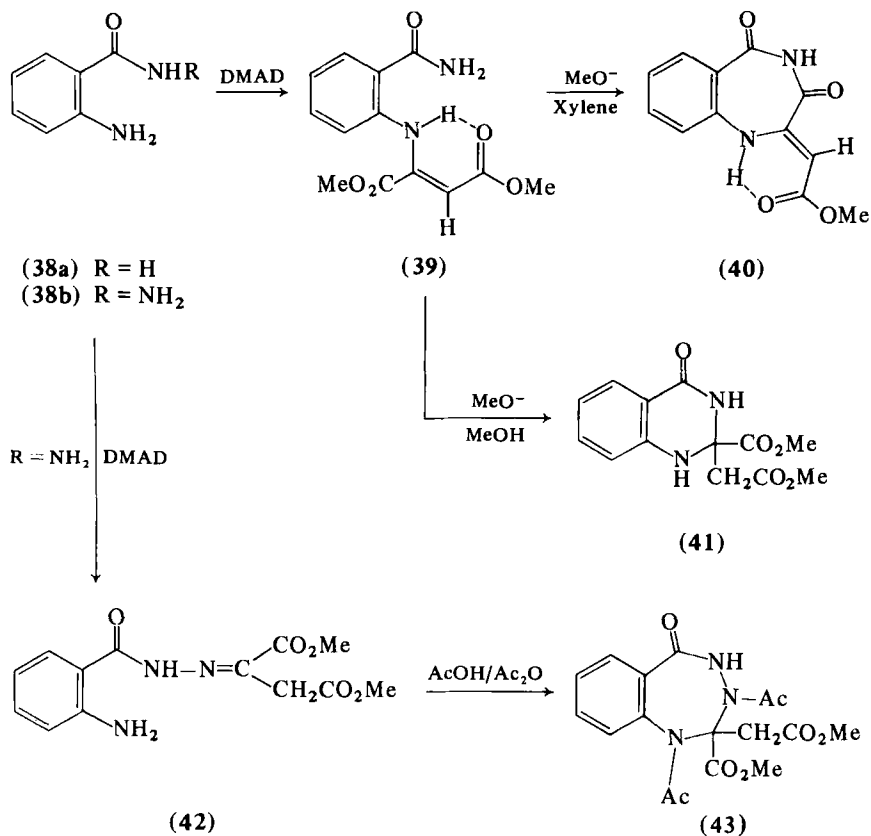
⁴⁷ N. D. Heindel and T. F. Lemke, *J. Heterocycl. Chem.* **3**, 389 (1966).

⁴⁸ N. D. Heindel, V. B. Fish, and T. F. Lemke, *J. Org. Chem.* **33**, 3997 (1968).

⁴⁹ T. F. Lemke, H. W. Snady, and N. D. Heindel, *J. Org. Chem.* **37**, 2337 (1972).

⁵⁰ W. P. Fives, Ph.D. Thesis, Lehigh Univ. (1971); *Diss. Abstr. B* **32**, 3849 (1972).

⁵¹ M. D. Nair, *Indian J. Chem.* **11**, 109 (1973).

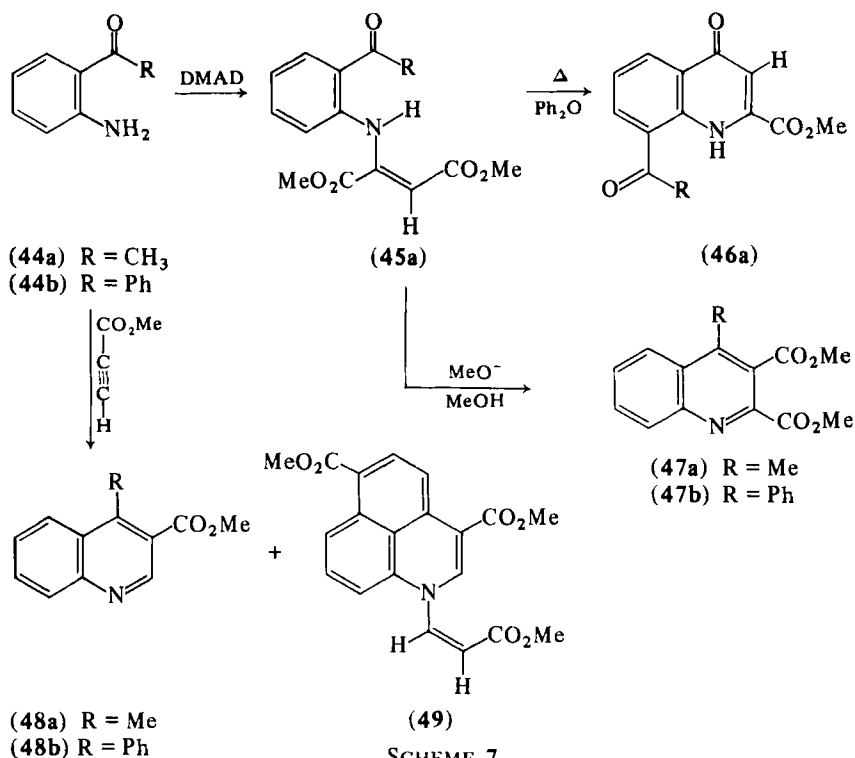


SCHEME 6

(43) (Scheme 6). Taylor and Heindel⁵² have reported two modes of cyclization in the case of an enamine adduct (45a) obtained from the reaction of *o*-aminoacetophenone (44a) with DMAD. In refluxing diphenyl ether, the enamine adduct (45a) gives 8-acetyl-2-carbomethoxy-4(1*H*)-quinolone (46a), whereas, under the influence of a strong base, the product formed is 2,3-dicarbomethoxy-4-methylquinoline (47a). The reaction of *o*-aminobenzophenone (44b), however, gives the quinoline derivative 47b.⁵² The reaction of 44a with methyl propiolate gives rise to a mixture of 3-carbomethoxy-4-methylquinoline (48a) and a product tentatively identified as 49 (Scheme 7).⁵³ On the other hand, the reaction of 44b with methyl propiolate gives only the quinoline derivative 48b.⁵³

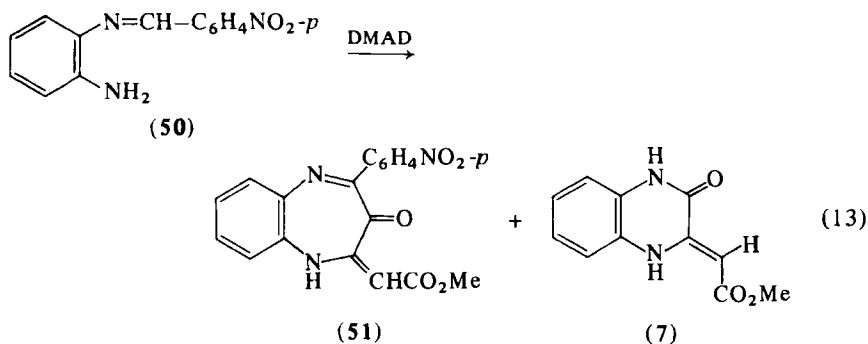
⁵² E. C. Taylor and N. D. Heindel, *J. Org. Chem.* **32**, 1666 (1967).

⁵³ N. D. Heindel, P. D. Kennewell, and C. J. Ohnmacht, *J. Org. Chem.* **34**, 1168 (1969).



SCHEME 7

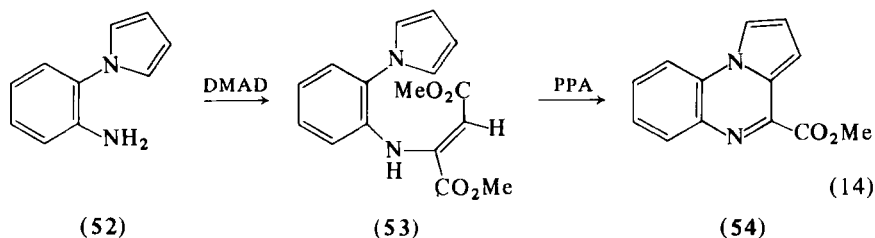
A mixture of benzodiazepinone (51) and tetrahydroquinoxaline derivative (7) has been observed in the reaction of *p*-nitrobenzal-*o*-phenylenediamine (50) with DMAD [Eq. (13)].⁵⁴ Nagarajan and co-workers⁵⁵ have reported the reaction of 1-(*o*-aminophenyl)pyrrole (52) with DMAD giving the corresponding enamine adduct (53), which in



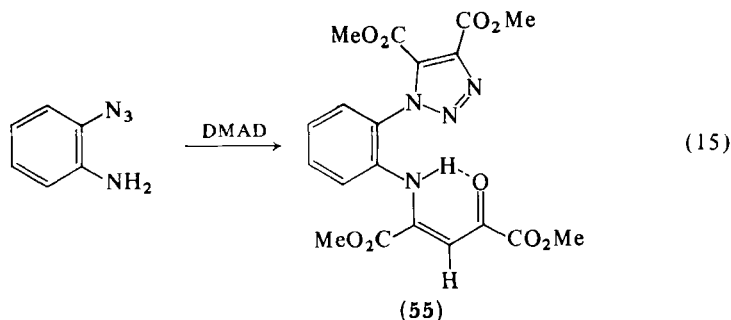
⁵⁴ S. K. Khetan and M. V. George, unpublished results.

⁵⁵ K. Nagarajan, V. R. Rao, and A. Venkateswarlu, *Indian J. Chem.* 10, 344 (1972).

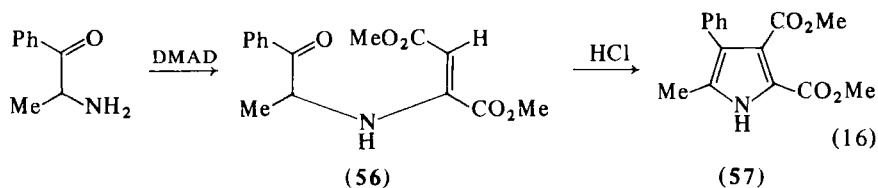
presence of polyphosphoric acid is cyclized to a pyrrolo[1,2-*a*]-quinoxaline (54) [Eq. (14)]. Similarly, the reaction of 52 with diethyl acetylenedicarboxylate gives the corresponding derivatives of 53 and 54.



In the reaction of *o*-azidoaniline with DMAD, it has been observed that both the amino and azido groups participate, giving rise to dimethyl 2-(4,5-dicarboxymethoxy-1,2,3-triazol-1-yl)anilino-fumarate (55) [Eq. (15)].⁵⁶



Hendrickson and co-workers⁴³ have used the reaction of α -amino-ketones with acetylenic esters for synthesizing pyrrole derivatives. Thus, in the reaction of α -aminopropiophenone with DMAD, an intermediate enamine adduct (56) is formed, which ultimately gives rise to the pyrrole 57 in presence of methanolic HCl [Eq. (16)]. Pandit and Huisman^{57,58} have shown the generality of this scheme in the synthesis of polycyclic pyrrole derivatives.

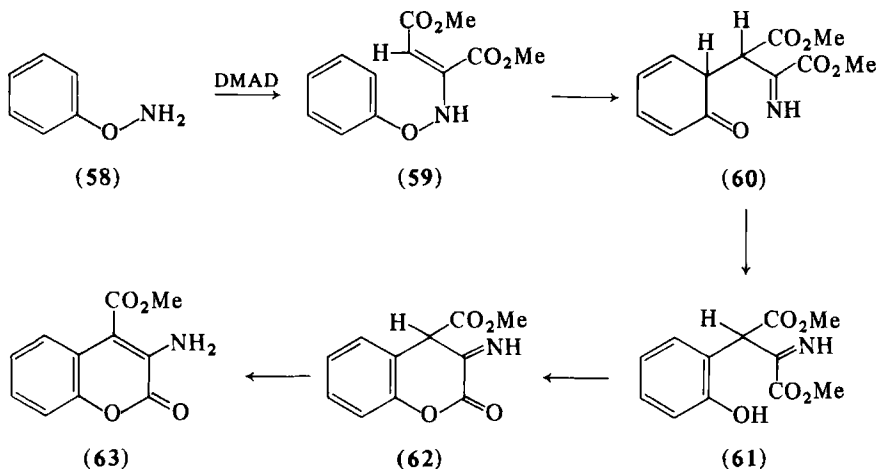


⁵⁶ S. K. Khetan and M. V. George, *Can. J. Chem.* **45**, 1993 (1967).

⁵⁷ U. K. Pandit and H. O. Huisman, *Rec. Trav. Chim.* **84**, 50 (1964) [*CA* **60**, 9231 (1964)].

⁵⁸ U. K. Pandit and H. O. Huisman, *Rec. Trav. Chim.* **85**, 311 (1966) [*CA* **65**, 10555 (1966)].

Sheradsky and Lewinter⁵⁹ have reported a fascinating transformation involving the reaction of *O*-arylhydroxylamine (58) and DMAD. The initially formed Michael adduct (59) undergoes valence tautomerism to 60, which gives rise to 3-amino-4-carbomethoxycoumarins (63), through the phenol intermediate 61 (Scheme 8).



SCHEME 8

B. SECONDARY AMINES

Secondary amines, such as dimethylamine,^{10r} diethylamine,⁶⁰ diisopropylamine,^{10r} dicyclohexylamine,^{10r} *N*-methylaniline,^{10r} aziridine,⁶¹⁻⁶⁵ and azetidine,⁶⁶ are reported to undergo *cis* addition to acetylenic esters, giving rise to simple 1 : 1 Michael adducts, in each case. These adducts have been successfully employed in the synthesis of different heterocyclic compounds.

Winterfeldt and co-workers⁶⁷⁻⁶⁹ have observed that *N*-allylmalesic ester derivatives (64) formed in the reaction of *N*-allylanilines with

⁵⁹ T. Sheradsky and S. Lewinter, *Tetrahedron Lett.* 3941 (1972).

⁶⁰ S. Ruhemann and A. V. Cunningham, *J. Chem. Soc.* 75, 954 (1899).

⁶¹ E. Winterfeldt and H. Preuss, *Chem. Ber.* 99, 450 (1966).

⁶² J. E. Dolfini, *J. Org. Chem.* 30, 1298 (1965).

⁶³ E. Winterfeldt and H. Preuss, *Angew. Chem.* 77, 679 (1965); *Angew. Chem., Int. Ed. Engl.* 4, 689 (1965).

⁶⁴ R. Huisgen, B. Giese, and H. Huber, *Tetrahedron Lett.* 1883 (1967).

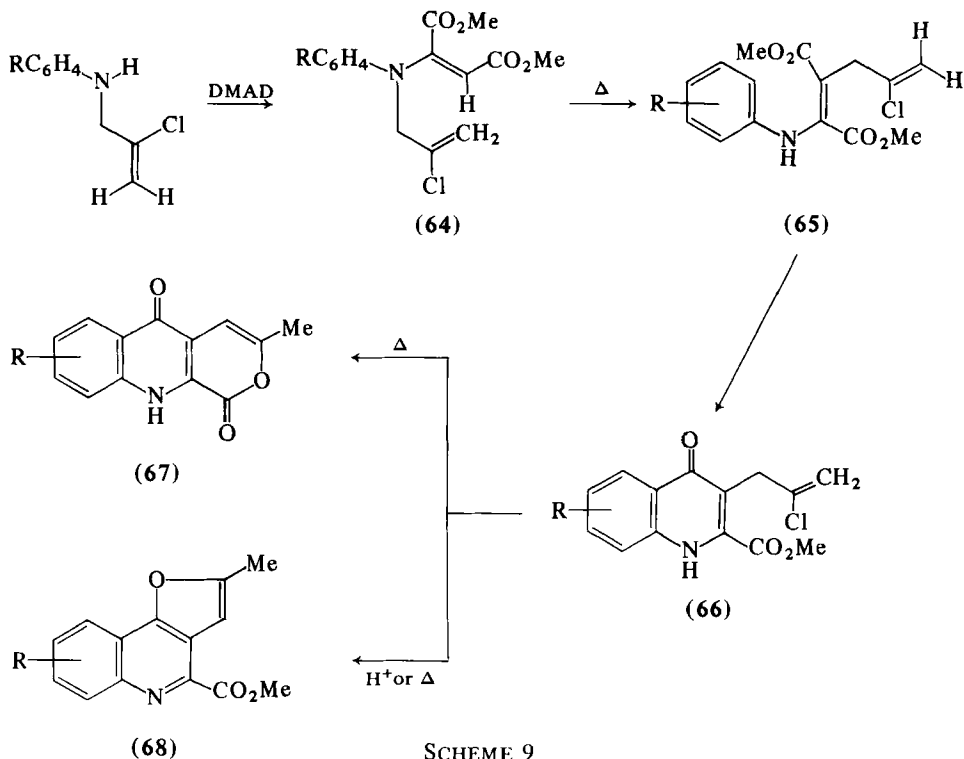
⁶⁵ A. Padwa and L. Hamilton, *Tetrahedron Lett.* 4363 (1965).

⁶⁶ T. Y. Chen, H. Kato, and M. Ohta, *Bull. Chem. Soc. Jap.* 39, 1618 (1966) [*CA* 13635 (1966)].

⁶⁷ G. Schmidt, Ph.D. Thesis, Technische Univ., Berlin (1970).

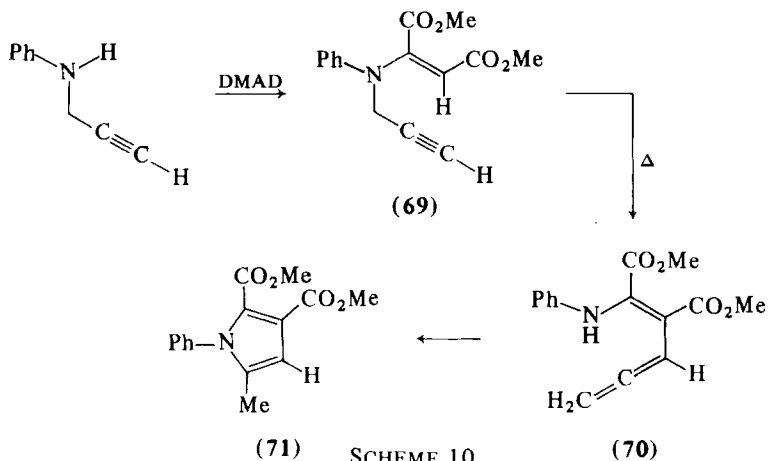
⁶⁸ E. Winterfeldt, *Fortschr. Chem. Forsch.* 16, 75 (1970) [*CA* 74, 86985 (1971)].

⁶⁹ G. Schmidt and E. Winterfeldt, *Chem. Ber.* 104, 2483 (1971).



SCHEME 9

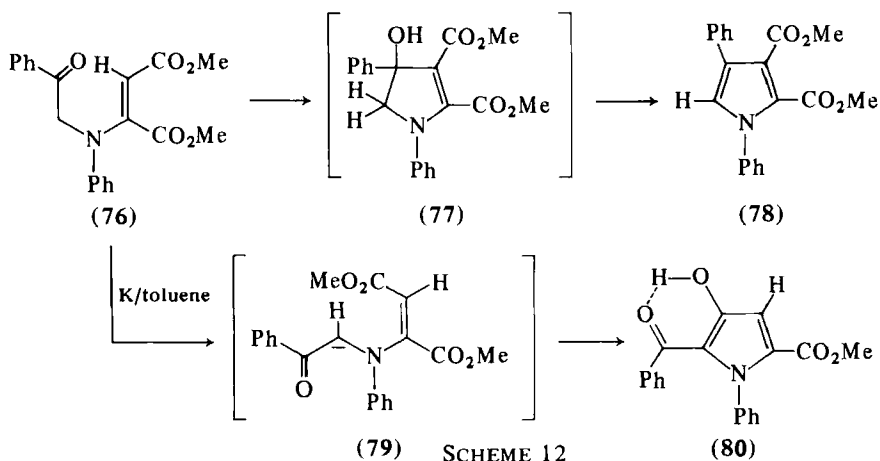
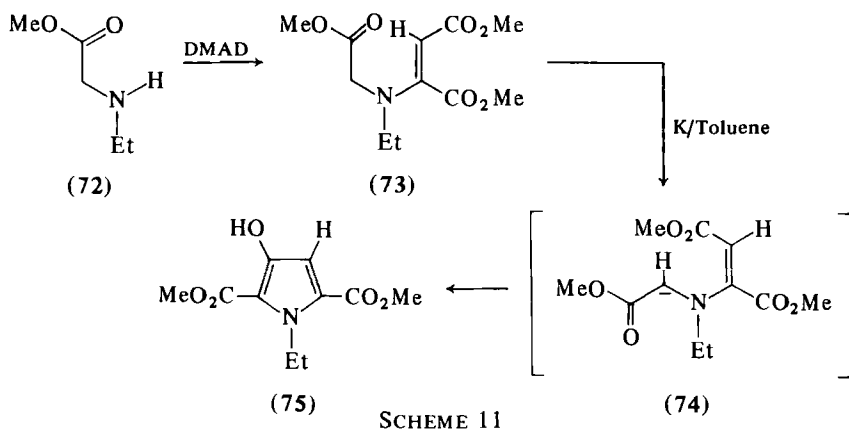
DMAD get thermally converted to quinolones (66), through a Cope rearrangement. These quinolones give rise to tricyclic heteroaromatic compounds, namely, pyrano[3,4-*b*]quinoline-1,5-diones (67) and furo[3,2-*c*]quinolines (68), depending on the reaction conditions (Scheme



SCHEME 10

9).⁷⁰ Similarly, the adducts of *N*-allylthiophenamines with DMAD lead to the formation of various tricyclic thiophene derivatives through hetero-Cope rearrangements.⁷¹ An analogous reaction of *N*-propynylaniline, on the other hand, leads to the formation of a pyrrole derivative (71) (Scheme 10).⁶⁷⁻⁶⁹

Winterfeldt and Dillinger⁷² have shown that methyl *N*-ethylglycinate (72) reacts with DMAD to give an enamine maleate (73), which undergoes a Dieckmann type of cyclization to give the pyrrole 75 (Scheme 11). Khetan and George⁷³ have studied the reaction of several



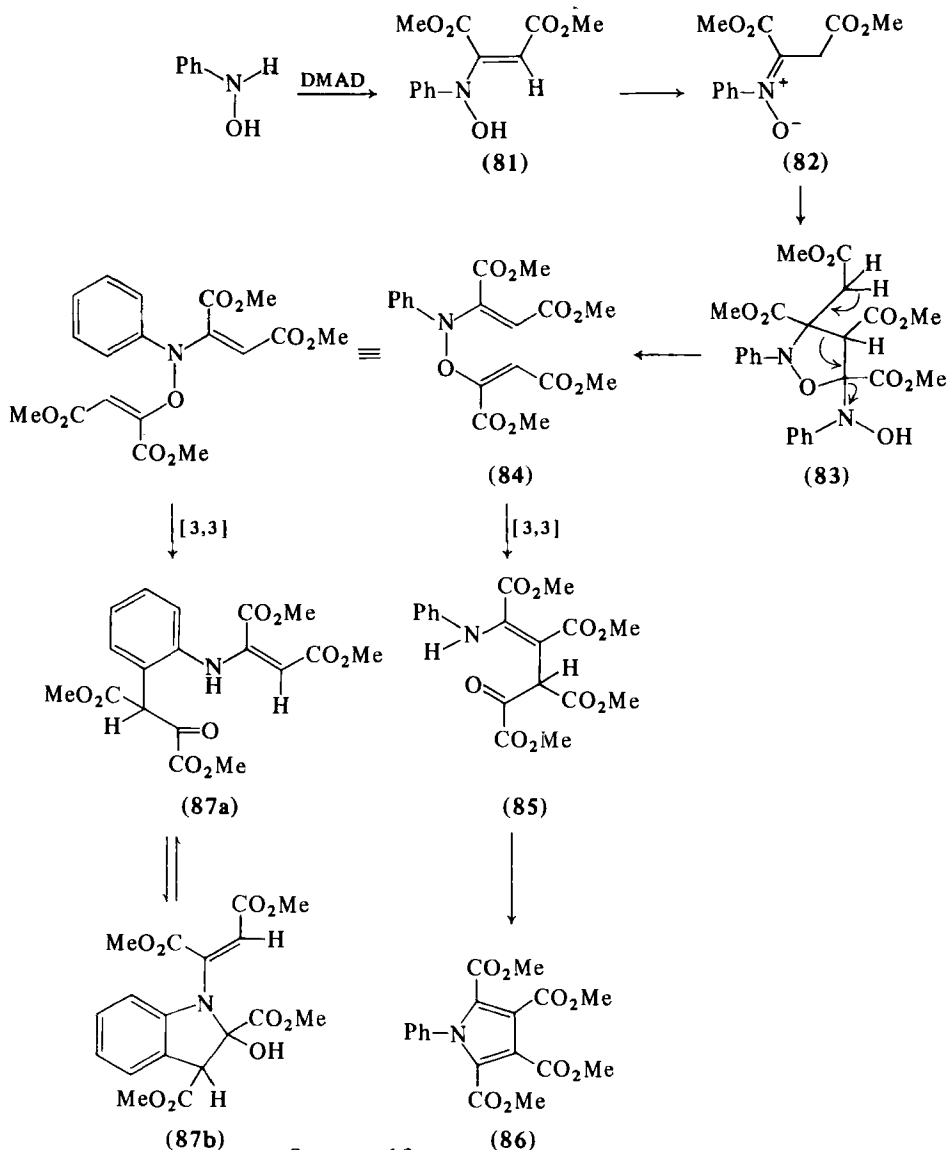
⁷⁰ S. Blechert, R. Gericke, and E. Winterfeldt, *Chem. Ber.* **106**, 355 (1973).

⁷¹ S. Blechert, R. Gericke, and E. Winterfeldt, *Chem. Ber.* **106**, 368 (1973).

⁷² E. Winterfeldt and H. J. Dillinger, *Chem. Ber.* **99**, 1558 (1966).

⁷³ S. K. Khetan and M. V. George, *Tetrahedron* **25**, 527 (1969).

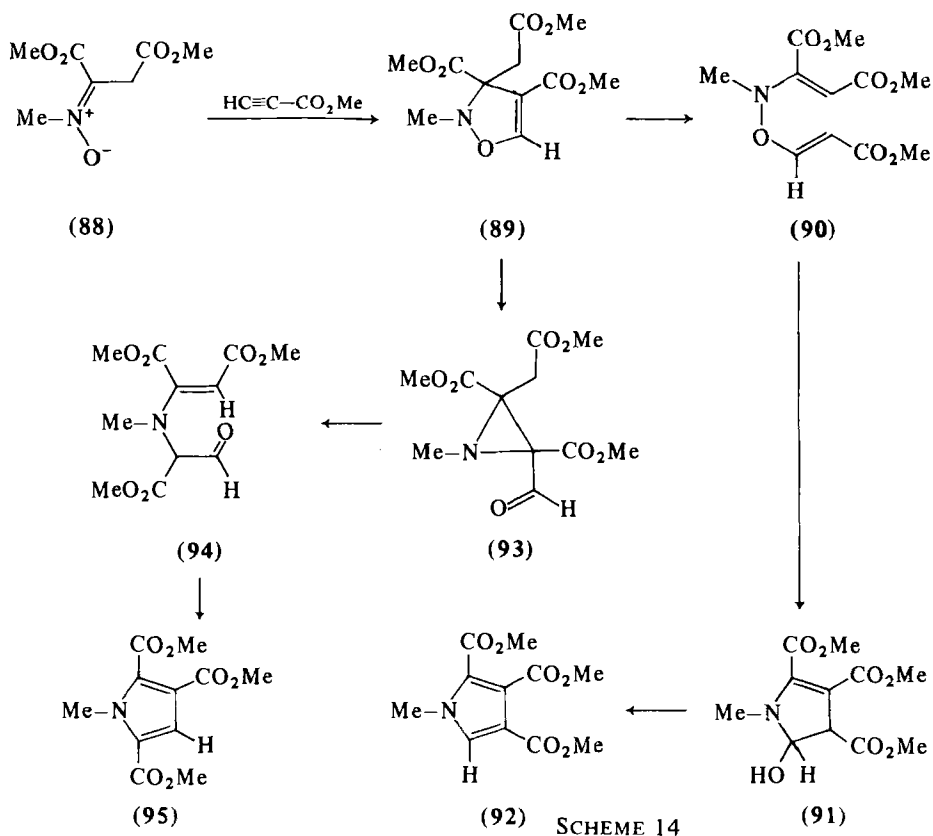
phenacylanilines with DMAD and have observed that phenacylanilino-maleates are formed in these reactions. The phenacylanilino-maleate (76), for example, undergoes an acid-catalyzed cyclization to give the pyrrole 78 whereas the Dieckmann cyclization of 76 yields the hydroxypyrrole 80 (Scheme 12).⁷³ Similarly, pyrrole derivatives are reported in the reaction of desylaniline with DMAD and methyl propiolate.⁷⁴



SCHEME 13

⁷⁴ D. S. James and P. E. Fanta, *J. Org. Chem.* **27**, 3346 (1962).

Agosta⁷⁵ had reported that tetramethyl *N*-phenylpyrroletetracarboxylate (**86**) is formed in the reaction of *N*-phenylhydroxylamine with DMAD. Winterfeldt and co-workers⁷⁶ have reinvestigated this reaction, and they have shown that the nitron **82** is formed initially, which goes through a dimeric species (**83**) to an intermediate (**84**). A sigmatropic rearrangement of **84** leads to **85**, which subsequently cyclizes to the pyrrole **86**. An alternative mode of rearrangement of **84** gives rise to **87a**, which can exist in equilibrium with **87b** (Scheme 13). Similarly, the reaction of a nitron (**88**) with either DMAD or methyl propiolate can ultimately lead to pyrrole derivatives. It has been shown that in the reaction of **88** with methyl propiolate, for example, an isoxazole derivative (**89**) is formed initially, which can give rise to either **92** or **95**, depending on the reaction pathway (Scheme 14).⁷⁷

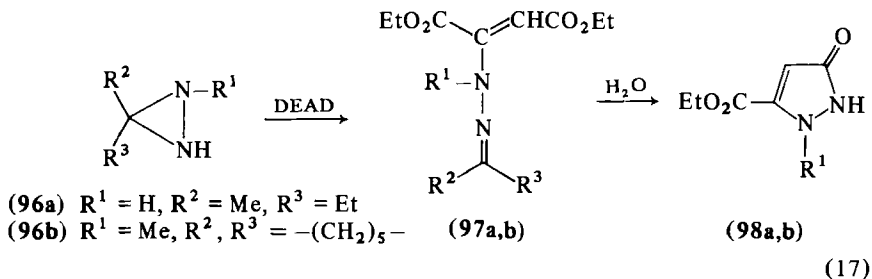


⁷⁵ W. C. Agosta, *J. Org. Chem.* **26**, 1724 (1961).

⁷⁶ E. Winterfeldt, W. Krohn, and H. U. Stracke, *Chem. Ber.* **102**, 2346 (1969).

⁷⁷ G. Schmidt, H. U. Stracke, and E. Winterfeldt, *Chem. Ber.* **103**, 3196 (1970).

Diaziridines **96a** and **96b** react with diethyl acetylenedicarboxylate to yield oily products, presumed to be **97a** and **97b**. These have been characterized by hydrolyzing them to the known pyrazolinones **98a** and **98b**, respectively [Eq. (17)].⁷⁸ A similar observation has been made in the reaction of 1-methyl-3,3-pentamethylenediaziridine (**96b**) with ethyl propiolate. The reaction of 3,3-pentamethylenediaziridine with ethyl propiolate, on the other hand, yields a simple 1 : 1 Michael adduct.⁷⁸



C. TERTIARY AMINES (ALIPHATIC)

Trialkylamines are known to add to acetylenic esters in the presence of their salts to give dialkylaminomaleates.⁷⁹ Winterfeldt⁸⁰ has studied the reaction of various tertiary amines with methyl propiolate and has shown that these amines can be used as catalysts for additions to activated carbon-carbon triple bonds. The reactions of a few tertiary amines containing other functional groups, as in methyl *N,N*-diethylglycinate and ω -diethylaminoacetophenone, with acetylenic esters has been investigated. ω -Diethylaminoacetophenone, for example, reacts with DMAD in dimethyl sulfoxide to give the pyrrole (**101**) (Scheme 15). An analogous reaction has been observed when ω -diethylaminoacetophenone is treated with methyl propiolate.⁸⁰

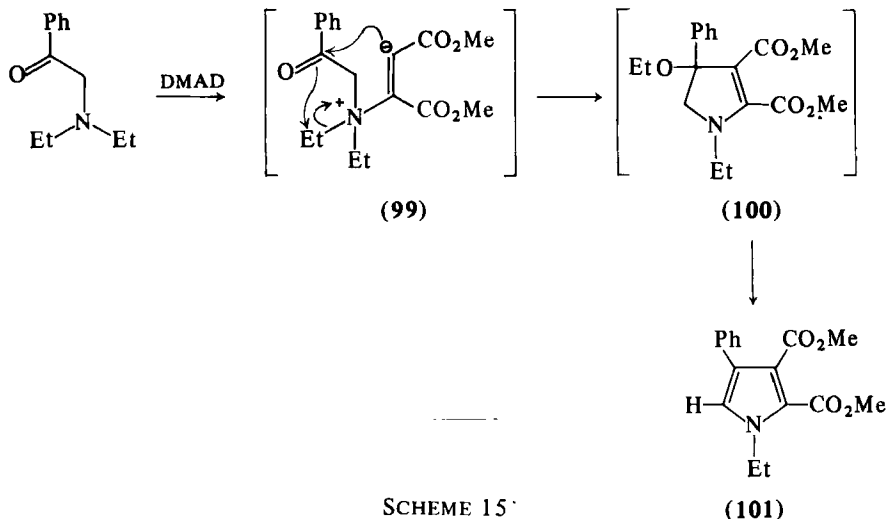
Winterfeldt and Krohn⁸¹ have shown that the reaction of *N,N*-diethylhydroxylamine with DMAD proceeds through an *N*-oxide intermediate (**102**), which gives rise to a mixture of products like the nitrene **104**, the azetidine **105**, and the hydroxylamine derivative **106** (Scheme 16).

⁷⁸ H. W. Heine, T. R. Hoye, P. G. Williard, and R. C. Hoye, *J. Org. Chem.* **38**, 2984 (1973).

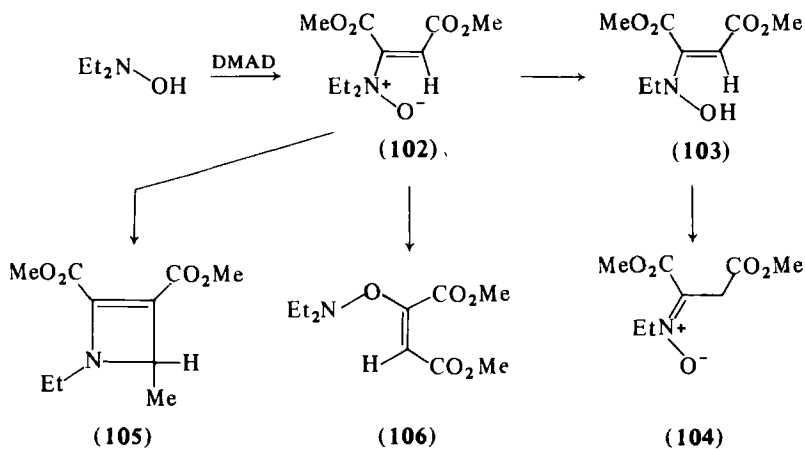
⁷⁹ R. J. Alaimo and D. G. Farnum, *Can. J. Chem.* **43**, 700 (1965).

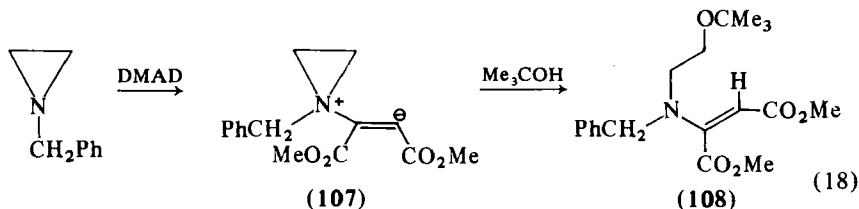
⁸⁰ E. Winterfeldt, *Chem. Ber.* **97**, 1952 (1964).

⁸¹ E. Winterfeldt and W. Krohn, *Chem. Ber.* **102**, 2336 (1969).

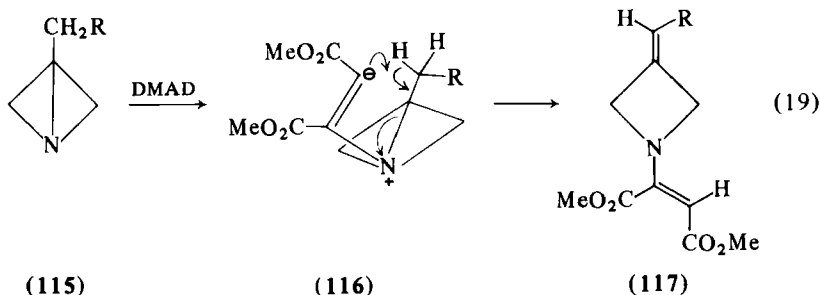


Aziridines react with acetylenic esters to give products which arise through either a C–N or C–C bond cleavage. In the reaction of *N*-benzylaziridine with DMAD in *t*-butanol, for example, C–N bond cleavage occurs to give the ether derivative **108** [Eq. (18)].⁷² However, in a great majority of cases, aziridines undergo facile C–C bond cleavage to give the corresponding azomethine ylides, which then undergo 1,3-dipolar cycloaddition reactions with acetylenic esters, leading to pyrrole

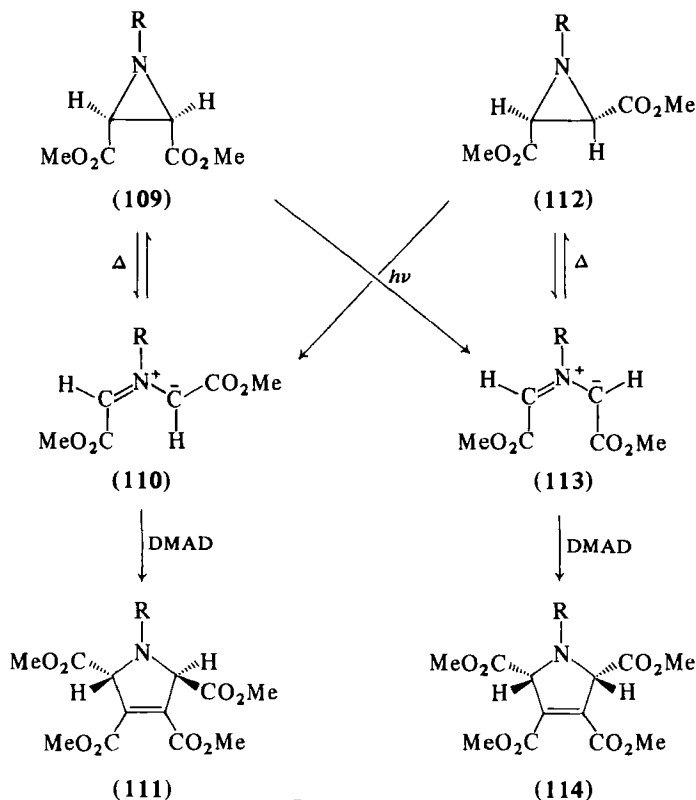




derivatives.⁸² Huisgen and co-workers^{82a} have shown that the ring-opening reactions of aziridines proceed through a symmetry-allowed conrotatory mode under thermal conditions, whereas they proceed through a disrotatory mode photochemically. Thus, they have found that the thermal opening of dimethyl 1-arylaziridine-2,3-*cis*-dicarboxylate (109) leads to the intermediate 110, which reacts with DMAD in a stereospecific manner leading to the pyrroline derivative 111. Under photochemical conditions, however, 109 leads to the intermediate 113, which gives rise to the isomeric pyrroline derivative 114 on reaction with DMAD. Similarly, the thermal and photochemical



⁸² For some of the reactions of aziridines, see: (a) J. W. Lown, *Rec. Chem. Progr.*, **32**, 51 (1971); (b) J. W. Lown and K. Matsumoto, *Yuki Gosei Kagaku Shi* **29**, 760 (1971) [*CA* **75**, 140563 (1971)]; (c) M. Kiyoshi, *Kagaku No Ryoiki* **27**, 148 (1973) [*CA* **79**, 42253 (1973)]; (d) H. W. Heine and J. Peavy, *Tetrahedron Lett.*, 3123 (1965); (e) H. W. Heine, R. Peavy, and A. J. Durbetaki, *J. Org. Chem.* **31**, 3924 (1966); (f) R. Huisgen, W. Scheer, G. Szeimies, and H. Huber, *Tetrahedron Lett.*, 397 (1966); (g) R. Huisgen, W. Scheer, and H. Huber, *J. Amer. Chem. Soc.* **89**, 1753 (1967); (h) A. Padwa and L. Hamilton, *J. Heterocycl. Chem.* **4**, 118 (1967); (i) S. Oida and E. Ohki, *Chem. Pharm. Bull.* **16**, 764 (1968) [*CA* **69**, 67261 (1968)]; (j) H. W. Heine, A. B. Smith, and J. D. Bower, *J. Org. Chem.* **33**, 1096 (1968); (k) S. Oida and E. Ohki, *Chem. Pharm. Bull.* **17**, 2461 (1969) [*CA* **72**, 78780 (1970)]; (l) H. W. Heine and R. P. Henzel, *J. Org. Chem.* **34**, 171 (1969); (m) R. Huisgen, W. Scheer, H. Mäder, and E. Brunn, *Angew. Chem., Int. Ed. Engl.* **8**, 604 (1969); (n) J. A. Deyrup, *J. Org. Chem.* **34**, 2724 (1969); (p) T. DoMinh and A. M. Trozzolo, *J. Amer. Chem. Soc.* **92**, 6997 (1970); (q) J. W. Lown and K. Matsumoto, *Can. J. Chem.* **48**, 2215 (1970); (r) P. B. Woller and N. H. Cromwell, *J. Org. Chem.* **35**, 888 (1970); (s) J. H. Hall, R. Huisgen, C. H. Ross, and W. Scheer, *Chem. Commun.* 1188 (1971); (t) A. Padwa and E. Glazer, *J. Amer. Chem. Soc.* **94**, 7788 (1972).



SCHEME 17

openings of dimethyl 1-arylaziridine-2,3-*trans*-dicarboxylate (112) lead to the intermediates 113 and 110, respectively (Scheme 17).

Funke⁸³ has observed an interesting reaction of 1-azabicyclo[1.1.0]-butane derivative (115) with DMAD in which an azetidine derivative (117) is formed, presumably through the intermediate 116 [Eq. (19)].

D. HYDRAZINES, HYDRAZONES, AND HYDRAZIDES

a. *Hydrazines*. Rothenburg⁸⁴ has shown that ethyl pyrazol-5-one-3-carboxylate (119a) is formed in the reaction of hydrazine hydrate with diethyl acetylenedicarboxylate [Eq. (20)]. Similar reactions of hydrazine with methyl⁸⁴ and ethyl propiolates,⁸⁵ ethyl methylpropiolate,⁸⁶ ethyl

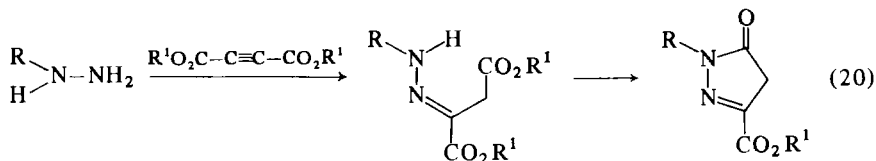
⁸³ W. Funke, *Chem. Ber.* **102**, 3148 (1969).

⁸⁴ (a) R. V. Rothenburg, *Ber.* **26**, 1719 (1893); (b) *Ber.* **26**, 1722 (1893).

⁸⁵ W. Wislicenus, *Ann.* **246**, 306 (1888); **277**, 375 (1893).

⁸⁶ (a) A. F. Oskerko, *Mem. Inst. Chem. Ukrain. Acad. Sci.* **4**, 195 (1937) [*CA* **32**, 3334 (1938)]; (b) *J. Gen. Chem. USSR* **8**, 330 (1938) [*CA* **32**, 5377 (1938)].

phenylpropiolate,⁸⁷ methyl 5-bromo-2-furylpropiolate,⁸⁸ and aryl propiolic acids⁸⁹ give rise to the corresponding pyrazolones. Buchner^{10a} has shown that phenylhydrazine reacts with DMAD to form a 1 : 1 adduct (118b), which under basic conditions gives the *N*-phenylpyrazolone (119b) [Eq. (20)]. Recently, it has been shown that the adduct 118b exhibits an imine-enamine type of tautomerism and that it exists predominantly in the imine form.⁹⁰ In the reaction of 2-hydrazinopyridine and 2-hydrazinoquinoline with DMAD, the products formed



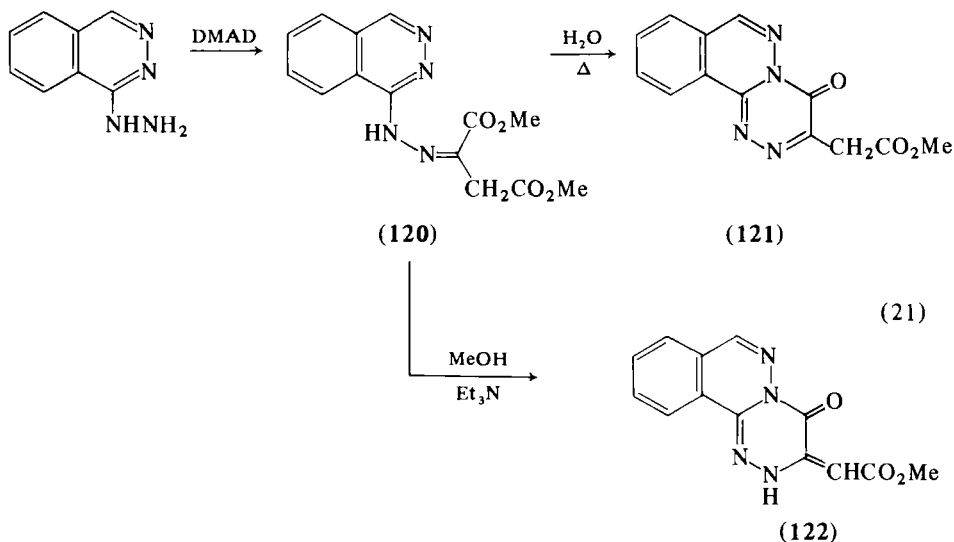
(a) R = H

(118a) R = H; R¹ = Et(119a) R = H; R¹ = Et

(b) R = Ph

(118b) R = Ph; R¹ = Me(119b) R = Ph; R¹ = Me

are the corresponding 3-carbomethoxypyrazolin-5-ones, indicating thereby that the tertiary nitrogen in these cases is not participating in the reactions.^{91,92} In the reaction of 1-hydrazinophthalazine, the initially



⁸⁷ T. Curtius and E. Kenngott, *J. Prakt. Chem.* 112, 314 (1926) [CA 20, 2157 (1926)].

⁸⁸ L. I. Vereshchagin, S. P. Korshunov, S. L. Aleksandrova, and R. L. Bol'shevskaya, *Zh. Org. Khim.* 1, 960 (1965) [CA 63, 6944 (1965)].

⁸⁹ F. G. Baddar, M. F. El-Newaihy, and M. R. Salem, *J. Chem. Soc., C*, 836 (1969).

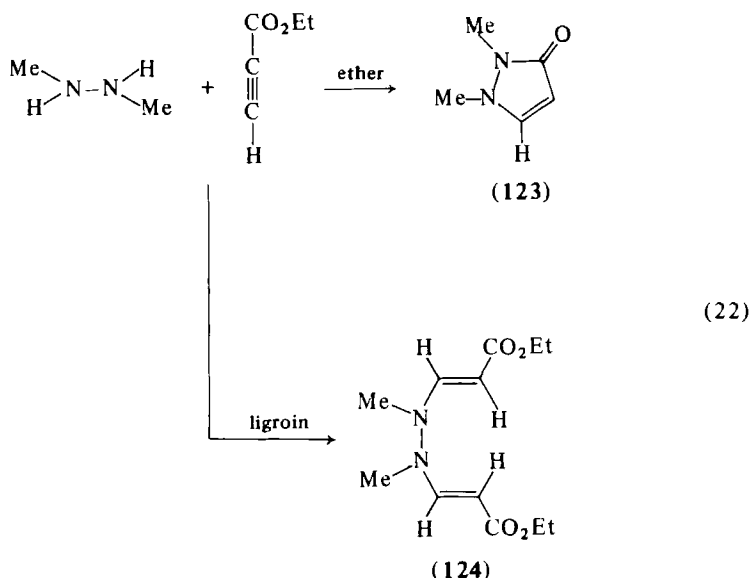
⁹⁰ N. D. Heindel, P. D. Kennewell, and M. Pfau, *J. Org. Chem.* 35, 80 (1970).

⁹¹ M. D. Nair, *Indian J. Chem.* 9, 104 (1971).

⁹² M. Brugger, H. Wamhoff, and F. Korte, *Ann.* 757, 100 (1972).

formed 1:1-adduct (120), which exists in the imine form, is transformed into the triazinone 121 or 122, depending on the reaction conditions [Eq. (21)].⁹³

1,2-Dimethylhydrazine reacts with ethyl propiolate to give 1,2-dimethylpyrazol-5-one (123) in ether solvent, whereas the hydrazine derivative (124) is formed when the reaction is carried out in ligroin [Eq. (22)].⁹⁴ The reactions of 1,1-diphenylhydrazine and of 1-phenyl-1-benzylhydrazine with DMAD are known to give 1:1-enamine adducts.^{91,95} Similarly, the reaction of hydrazobenzene with DMAD gives an enamine adduct (125), which is transformed into several products depending on the reaction conditions. Thus, in glacial acetic acid, 1,2-diphenyl-3-carbomethoxy-5-pyrazolone (126) is formed, whereas in xylene dimethyl indole-2,3-dicarboxylate (127) is obtained. However, when the reaction is carried out in pyridine, the product formed is 2-hydroxy-3-anilino-4-carbomethoxyquinoline (128) (Scheme 18).⁹⁶ The reactions of several substituted hydrazobenzenes have also been studied to show the generality of these reactions.^{97,98}



⁹³ D. J. Le Count and A. T. Greer, *Tetrahedron Lett.*, 2905 (1973).

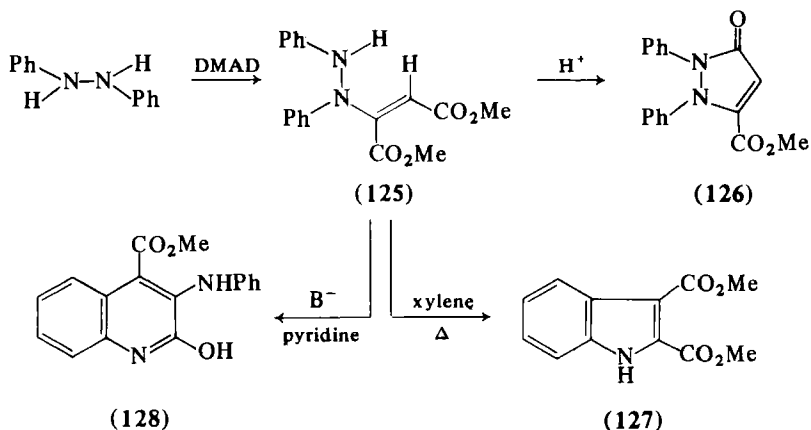
⁹⁴ F. Lingens and H. S. Bernlöhner, *Ann.* **686**, 134 (1965).

⁹⁵ O. Diels and J. Reese, *Ann.* **519**, 147 (1935) [*CA* **29**, 7333 (1935)].

⁹⁶ O. Diels and J. Reese, *Ann.* **511**, 168 (1934) [*CA* **28**, 5453 (1934)].

⁹⁷ E. H. Huntress and W. H. Hearon, *J. Amer. Chem. Soc.* **63**, 2762 (1941).

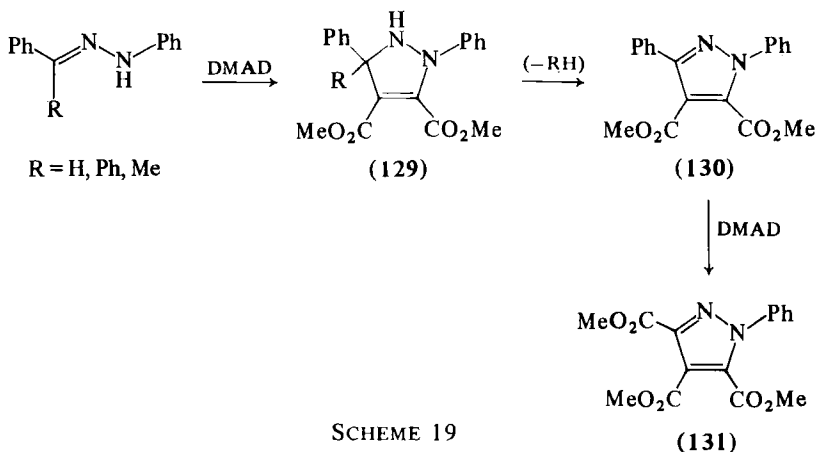
⁹⁸ E. H. Huntress, J. Bornstein, and W. H. Hearon, *J. Amer. Chem. Soc.* **78**, 2225 (1956).



SCHEME 18

The reaction of aroylhydrazines with DMAD gives rise to the hydrazones of oxaloacetic ester, which undergo thermal transformation to the corresponding diaroylhydrazines.⁹⁹

b. *Hydrazones*. Ethyl 1,3,5-triphenylpyrazole-4-carboxylate has been reported to be formed in the reaction of benzaldehyde phenylhydrazone with ethyl phenylpropiolate.¹⁰⁰ In a detailed investigation, George and co-workers¹⁰¹ have shown that aldehyde phenylhydrazones react with DMAD, yielding a mixture of pyrazoles and pyrazolines. Thus, in the reaction of benzaldehyde phenylhydrazone with DMAD, products such as dimethyl 1,3-diphenylpyrazoline-4,5-dicarboxylate (129), dimethyl



SCHEME 19

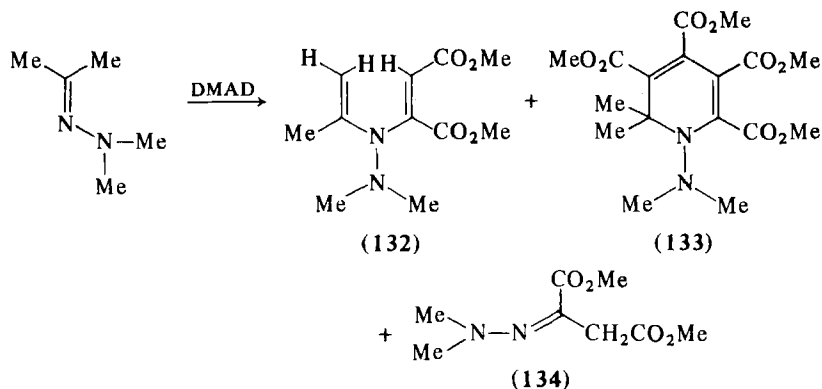
⁹⁹ M. N. Gudi, J. G. Hiriyakkanavar, and M. V. George, *Indian J. Chem.* **9**, 743 (1971).

¹⁰⁰ C. Musante, *Gazz. Chim. Ital.* **67**, 682 (1937) [CA **32**, 4580 (1938)].

¹⁰¹ M. K. Saxena, M. N. Gudi, and M. V. George, *Tetrahedron* **29**, 101 (1973).

1,3-diphenylpyrazole-4,5-dicarboxylate (**130**), and a small amount of trimethyl 1-phenylpyrazole-3,4,5-tricarboxylate (**131**) are formed. It has been suggested that the formation of **131** in this reaction may be due to the further reaction of the pyrazole **130** with excess of DMAD (Scheme 19). In the reactions of benzaldehyde methylhydrazone and of benzaldehyde benzylhydrazone, on the other hand, simple enehydrazine adducts have been reported.¹⁰² The reaction of ketone phenylhydrazones, such as acetophenone phenylhydrazone and benzophenone phenylhydrazone, are reported to give rise to the same pyrazole (**130**) formed in the reaction of benzaldehyde phenylhydrazone with DMAD. The formation of the pyrazole **130** in these cases has been rationalized in terms of the loss of benzene and methane molecules, respectively, from the initially formed pyrazolines (**129**) (Scheme 19).¹⁰¹

An interesting case of the addition of ketone hydrazone is observed in the reaction of acetone dimethylhydrazone with DMAD, wherein the initial nucleophilic attack is through the imino nitrogen, leading to products such as dimethyl *N*-isopropylidene-*N*-dimethylamino-2-aminomaleate (**132**) and the dihydropyridine derivative (**133**). A small amount of the dimethylhydrazone of oxaloacetic ester (**134**) has also been observed in this reaction (Scheme 20).¹⁰³



SCHEME 20

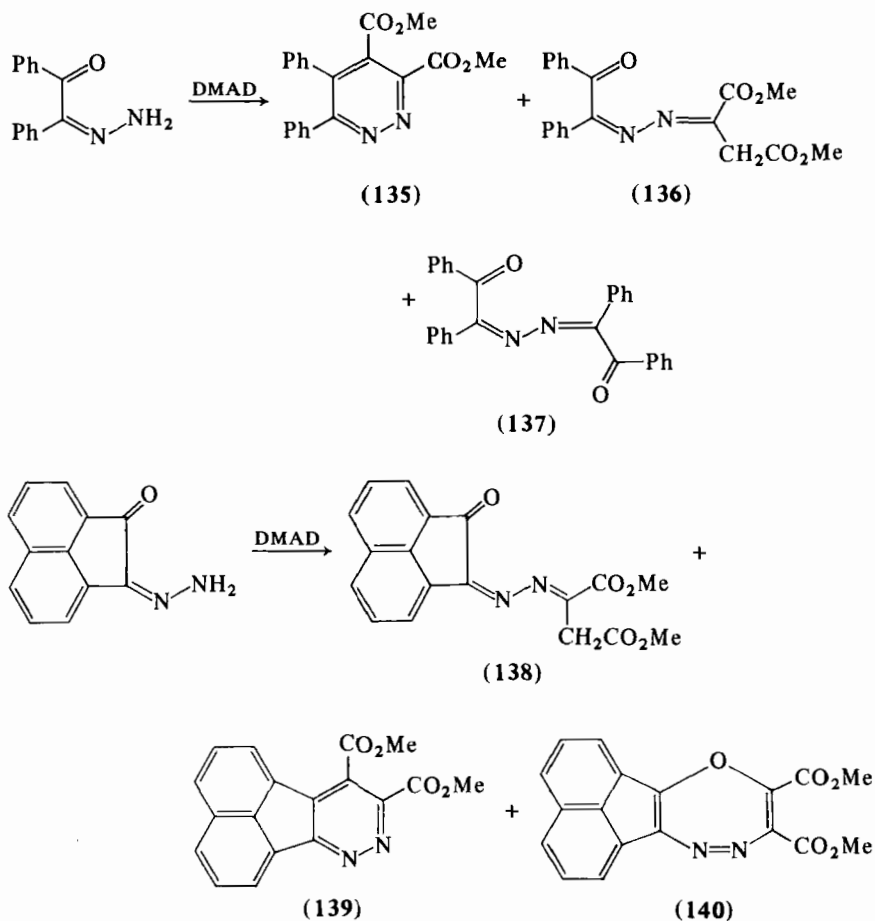
A convenient route to pyridazine derivatives is found in the reaction of monohydrazones of 1,2-diketones with DMAD. The reaction of benzil monohydrazone with DMAD, for example, gives a mixture of products consisting of dimethyl 5,6-diphenylpyridazine-3,4-dicarboxylate (**135**), benzil dimethyl oxaloacetate ketazine (**136**) and benzil bisketazine (**137**).¹⁰⁴ A similar reaction of acenaphthenequinone

¹⁰² W. Sucrow and M. Slopianka, *Chem. Ber.* **105**, 3807 (1972).

¹⁰³ S. F. Nelson, *J. Org. Chem.* **34**, 2248 (1969).

¹⁰⁴ R. K. Gupta and M. V. George, *Indian J. Chem.* **10**, 875 (1972).

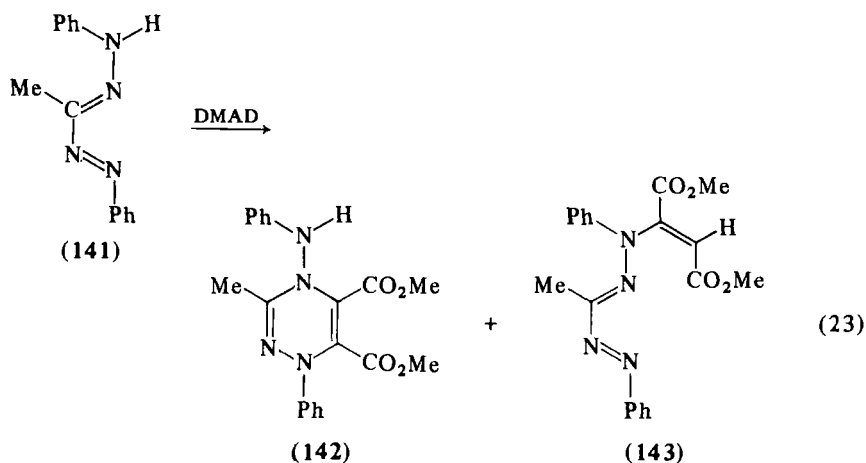
monohydrazone, on the other hand, gives products consisting of a 1 : 1 enehydrazine adduct (138), a pyridazine derivative (139), and an ox-adiazepine derivative (140) (Scheme 21).¹⁰⁴



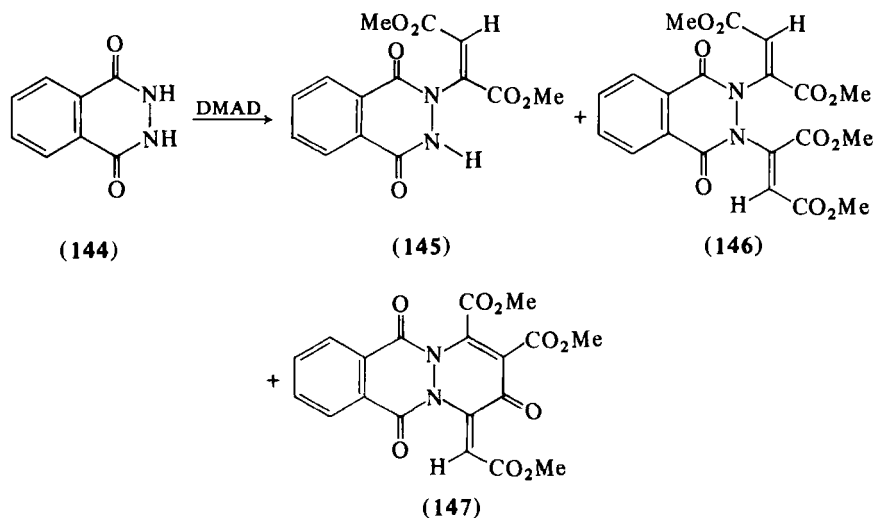
SCHEME 21

In the reaction of heterocyclic amidrazones with DMAD, condensed 1,2,4-triazinones have been reported.⁹² Cherkasov *et al.*¹⁰⁵ have studied the reaction of the formazan (141) with DMAD and have shown that the 1,3,4-dihydrotriazine derivative (142) and a 1 : 1 adduct (143) are formed in this reaction [Eq. (23)].

¹⁰⁵ V. M. Cherkasov, I. A. Nasyr, and V. T. Tsyba, *Khim. Geterotsikl. Soedin.*, 1704 (1970) [*CA* 74, 100003 (1971)].



c. *Hydrazides*. *N*-Acylhydrazones are formed in the reaction of monosubstituted hydrazides with DMAD.¹⁰⁶ Recently, it has been shown that several cyclic hydrazides react with DMAD to give simple 1 : 1 or 1 : 2 adducts or products derived from these initial adducts.¹⁰⁷ In the reaction of phthalhydrazide (144), for example, the products formed include dimethyl phthalhydrazidofumarate (145), *N*-(dimethylfumarato)-*N'*-(dimethylmaleato)phthalhydrazide (146), and a small amount of the cyclized product (147) (Scheme 22).



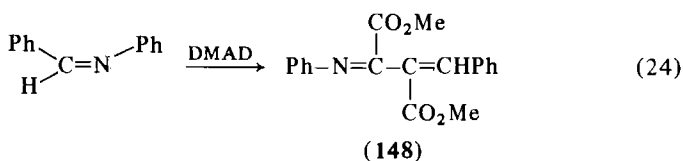
SCHEME 22

¹⁰⁶ J. W. Lown and J. C. N. Ma, *Can. J. Chem.* **45**, 953 (1967).

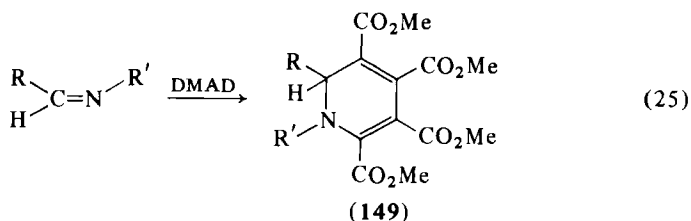
¹⁰⁷ M. N. Gudi and M. V. George, *Indian J. Chem.* **10**, 881 (1972).

E. SCHIFF'S BASES AND OXIMES

a. *Schiff's Bases*. A number of Schiff's bases have been allowed to react with acetylenic esters.¹⁰⁸⁻¹¹³ It has been found that the product depends largely on the nature of the substituents present on nitrogen. Snyder and co-workers¹⁰⁸ have observed the formation of α -benzal- α' -phenyliminosuccinate (**148**) from the reaction of benzalimine and DMAD [Eq. (24)]. It has been suggested that this product is formed



through the intermediacy of aniline, arising from the hydrolysis of the starting anil, under the reaction conditions. On the other hand, treatment of benzylidenemethylamine,^{109,112} cinnamylideneaniline,^{108,109,112} cinnamylidenemethylamine,¹⁰⁹ benzalbenzylamine,¹¹² and benzal-(2-phenylethylamine)^{111,112} give dihydropyridine derivatives (**149**) [Eq.



(25)]. The reaction of a ketimine, such as isopropylideneisopropylamine (150) with DMAD gives dimethyl *N*-(1-methylvinyl)isopropylaminomaleate (152), probably through the intermediate (151) [Eq. (26)].¹¹²

¹⁰⁸ H. R. Snyder, H. Cohen, and W. J. Tapp, *J. Amer. Chem. Soc.* **61**, 3560 (1939).

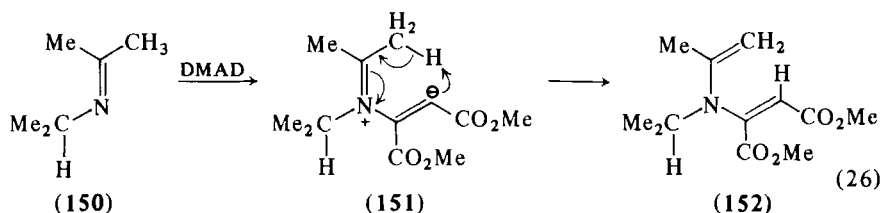
¹⁰⁹ J. M. F. Gagan, *J. Chem. Soc., C*, 1121 (1966).

¹¹⁰ A. DeSavignac and A. Lattes, *Bull. Soc. Chim. Fr.*, 4476 (1970) [CA 74, 75789 (1971)].

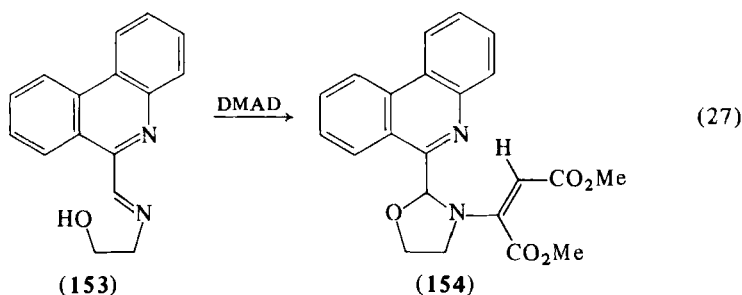
¹¹¹ M. Sakamoto and Y. Tomimatsu, *Yokugaku Zasshi* **90**, 1339 (1970) [*CA* **74**, 53468 (1971)].

¹¹² R. Huisgen and K. Herbig, *Ann.* **688**, 98 (1965).

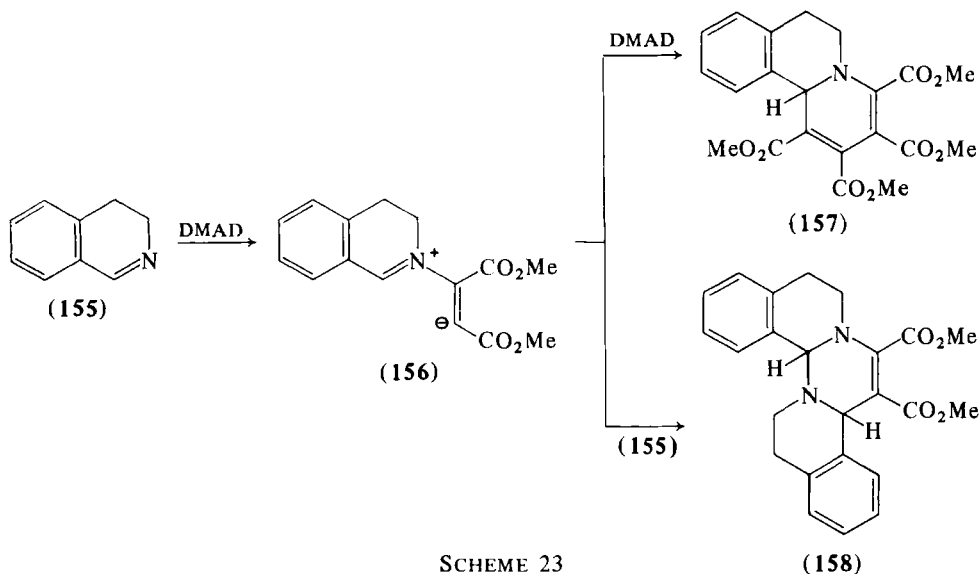
¹¹³ M. D. Nair, *Indian J. Chem.* **6**, 630 (1968).



An interesting reaction of a Schiff's base is observed in the case of **153**, formed from 9-phenanthridinecarboxaldehyde and ethanolamine, which gives the tetrahydrooxazole derivative (**154**), on treatment with DMAD [Eq. (27)].¹¹¹ Huisgen and Herbig¹¹² have observed that with



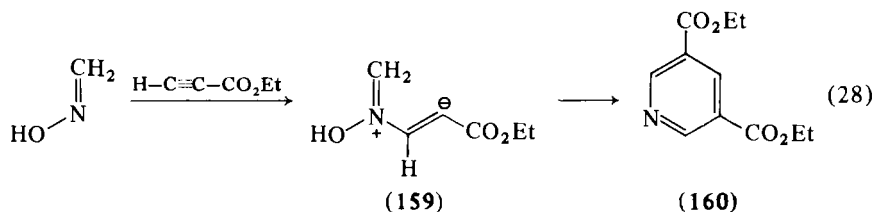
substrates like 3,4-dihydroisoquinoline (**155**), the normal addition product with excess of DMAD is the benzoquinolizine derivative (**157**), whereas the pyrimido[2,1-a:4,3-a']diisoquinoline derivative (**158**) is



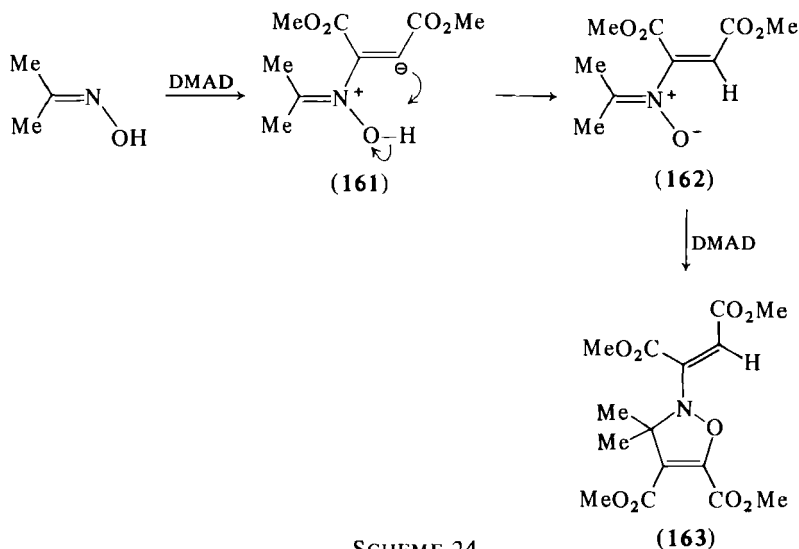
SCHEME 23

formed if the imine component (155) is in excess. Both these products (157 and 158) may arise through a 1,4-dipolar intermediate like 156 (Scheme 23). Nair¹¹³ has extended this reaction to other dihydroisoquinolines.

b. *Oximes*. An aldoxime such as formaldoxime reacts with ethyl propiolate to give a pyridine derivative (160), formed by the elimination of water from the initial dihydropyridine intermediate [Eq. (28)].¹¹⁴ This is in contrast to the reaction of formaldoxime with α,β -unsaturated



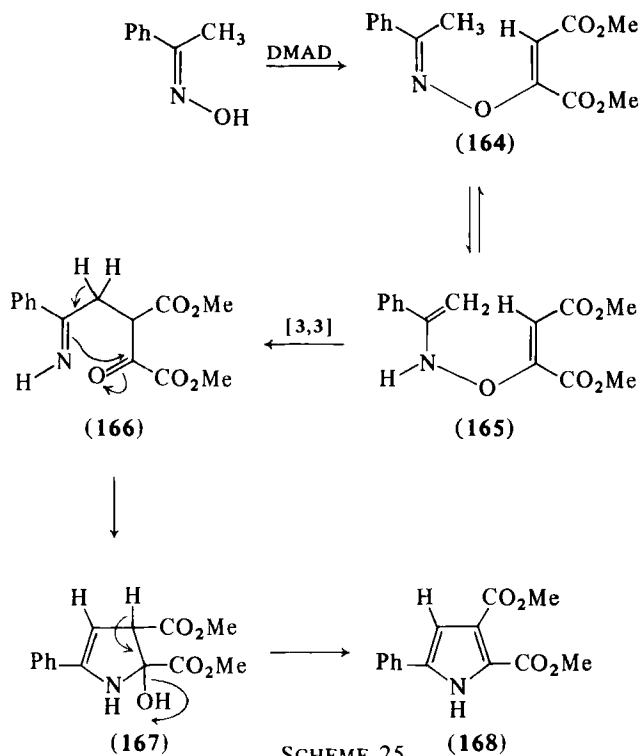
nitriles which gives isoxazoline derivatives. Winterfeldt and Krohn¹¹⁵ have studied the reaction of a few ketoximes such as acetone oxime and cyclohexanone oxime with DMAD and have shown that oxazoline derivatives are formed in these reactions. Thus, in the reaction of acetone oxime with DMAD, the oxazoline (163) is formed through a 1,3-dipolar addition of the initially formed nitrone (162) (Scheme 24).



SCHEME 24

¹¹⁴ M. Ochiai, M. Obayashi, and K. Morita, *Tetrahedron* **23**, 2641 (1967).

¹¹⁵ E. Winterfeldt and W. Krohn, *Angew. Chem., Int. Ed. Engl.* **6**, 709 (1967).



SCHEME 25

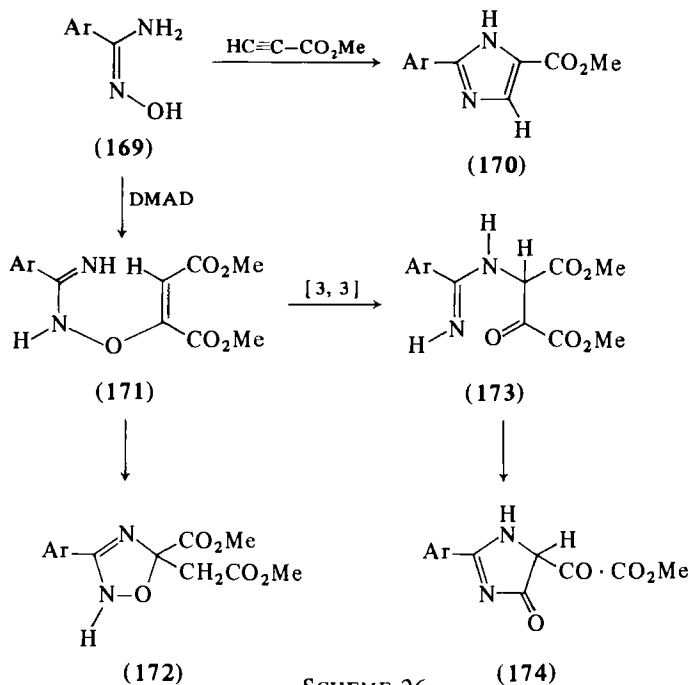
Sheradsky¹¹⁶ has found that the hydroxyl function of a ketoxime such as acetophenone oxime can be made to react with DMAD when the reaction is carried out in methanol with a basic catalyst, to give mixture of the fumarate and maleate isomers (164) in the ratio 2 : 1. This mixture on heating undergoes a hetero-Cope rearrangement followed by cyclization and dehydration to give dimethyl 5-phenylpyrrole-2,3-dicarboxylate (168) (Scheme 25). Similarly, Heindel and Chun¹¹⁷ have reported that vinyl ether adducts (171), obtained by the condensation of arylamide oximes with DMAD, get thermally converted into oxadiazolines (172) or imidazolinones (174), depending on the reaction conditions. A similar reaction occurs with aromatic amidoxime-methyl propiolate adducts to give imidazoles (170) (Scheme 26).¹¹⁸ 1,2,4-Dioxazoles have been reported to be formed in the reaction of hydroxamic acids with DMAD.^{50,119}

¹¹⁶ T. Sheradsky, *Tetrahedron Lett.*, 25 (1970).

¹¹⁷ N. D. Heindel and M. C. Chun, *Chem. Commun.*, 664 (1971).

¹¹⁸ N. D. Heindel and M. C. Chun, *Tetrahedron Lett.*, 1439 (1971).

¹¹⁹ F. M. W. Chen and T. P. Forrest, *Can. J. Chem.* 51, 1368 (1973).



SCHEME 26

F. ISOCYANIDES AND ISOCYANATES

a. *Isocyanides*. The reaction of isocyanides with acetylenic esters are of particular interest, in view of the variety of products that are formed in these cases. Winterfeldt and co-workers^{120,121} have reported that *t*-butyl isocyanide reacts with DMAD to give a mixture of 1 : 2 adducts 175 and 176. Jautelat and Ley,^{122,123} however, have observed that in presence of nickel halides or nickel acetate, *t*-butyl isocyanide reacts with DMAD, yielding the pyrrole derivatives 177 (Scheme 27). Suzuki and co-workers¹²⁴⁻¹²⁶ have shown that complex mixtures of products are formed in the reactions of 2,6-dimethylphenyl isocyanide and 4-bromo-2,6-dimethylphenyl isocyanide with DMAD. Some of these include the 2 : 1 adduct (178), the 3 : 1 adduct (179), and the product

¹²⁰ E. Winterfeldt, *Angew. Chem., Int. Ed. Engl.* **5**, 741 (1966).

¹²¹ E. Winterfeldt, D. Schumann, and H. J. Dillinger, *Chem. Ber.* **102**, 1656 (1969).

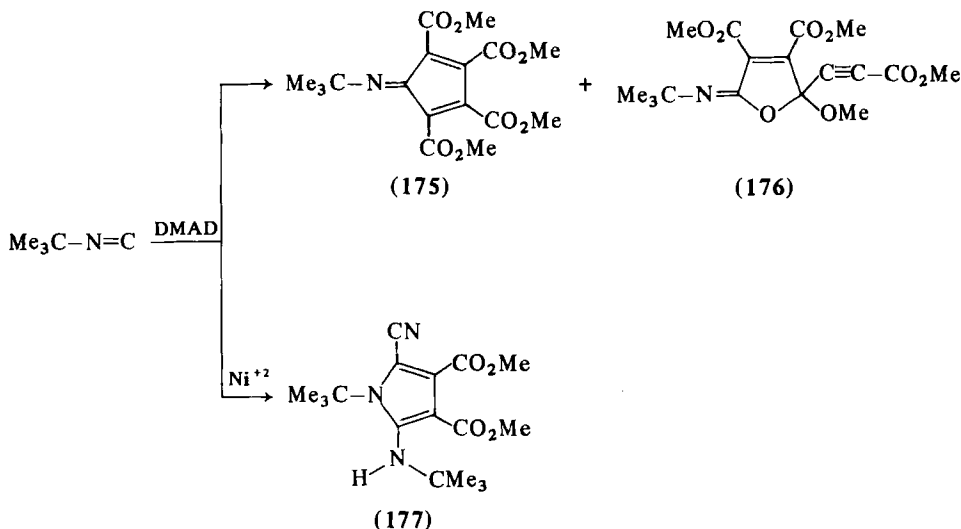
¹²² M. Jautelat and K. Ley, *Synthesis*, 593 (1970).

¹²³ M. Jautelat and K. Ley, German Patent, 1,951,965 (1971) [CA **75**, 35719 (1971)].

¹²⁴ T. Takizawa, N. Obata, Y. Suzuki, and T. Yanagida, *Tetrahedron Lett.*, 3407 (1969).

¹²⁵ Y. Suzuki, N. Obata, and T. Takizawa, *Tetrahedron Lett.*, 2667 (1970).

¹²⁶ Y. Suzuki and Y. Iitaka, *Bull. Chem. Soc. Jap.* **44**, 56 (1971) [CA **74**, 92298 (1971)].



SCHEME 27

(180) derived from 179 through the addition of water. In addition, a 2 : 3 adduct (183) is obtained, which can be isomerized to 184 on heating to around 150° (Scheme 28).

George and co-workers¹²⁷ have investigated the reaction of cyclohexyl isocyanide (185) with DMAD and have shown that a major constituent of the product mixture is the 2 : 3 adduct (186) formed through a [6 + 4] addition of the initially formed intermediate (182) with the dipolar species (181, R = cyclohexyl). Thermal isomerization of 186 in refluxing xylene results in an isomeric spiro compound (187), whereas at higher temperatures, other valence isomers of 186 are formed (Scheme 29).^{127,128} Winterfeldt had earlier isolated a 1 : 2 adduct (188) from the reaction of cyclohexyl isocyanide with DMAD.^{120,121} The reaction of some alkyl and aryl isocyanides with acetylenic esters in protic solvents, such as methanol, has been reported to give open-chain adducts with the incorporation of one or two solvent molecules.^{129,130}

b. *Isocyanates*. An example of the reaction of isocyanates with acetylenic esters is found in the reaction of benzoyl isocyanate (189) with ethyl propiolate to give an azetidinone derivative (190) [Eq. (29)].¹³¹

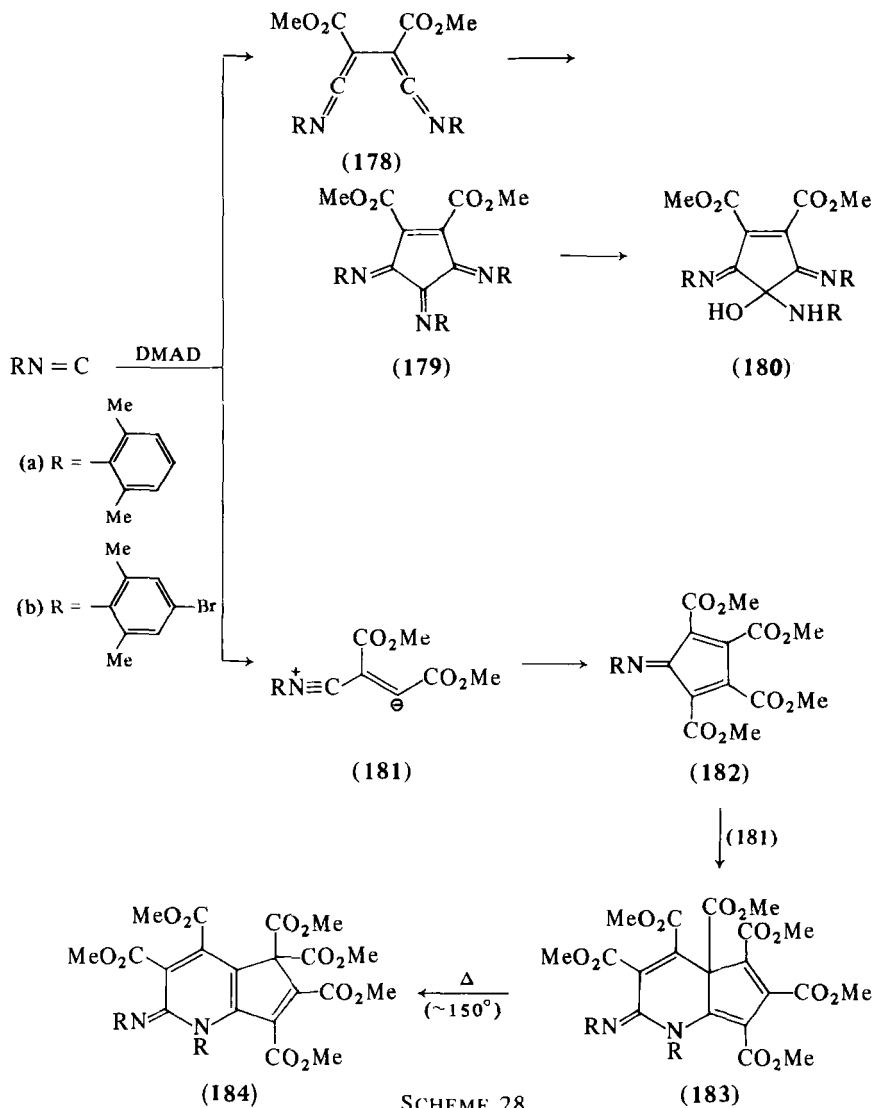
¹²⁷ M. V. George, J. G. Hiriyakkanavar, and M. K. Saxena, unpublished results.

¹²⁸ J. Z. Gougoutas and W. Saenger, *J. Org. Chem.* **36**, 3632 (1971).

¹²⁹ T. R. Oakes and D. J. Donovan, *J. Org. Chem.* **38**, 1319 (1973).

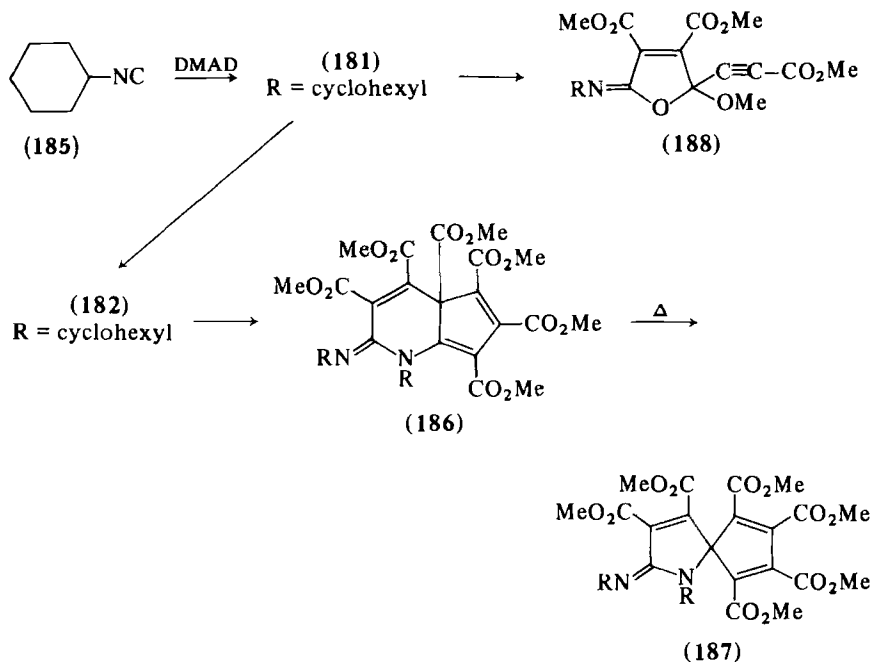
¹³⁰ T. Saegusa, Y. Ito, S. Tomita, H. Kinoshita, and T. Taka-ishi, *Tetrahedron* **27**, 27 (1971).

¹³¹ B. A. Arbuzov, N. N. Zbova and F. B. Balabanova, *Izv. Akad. Nauk SSSR, Ser. Khim.* 1570 (1970) [*CA* **74**, 76350 (1971)].

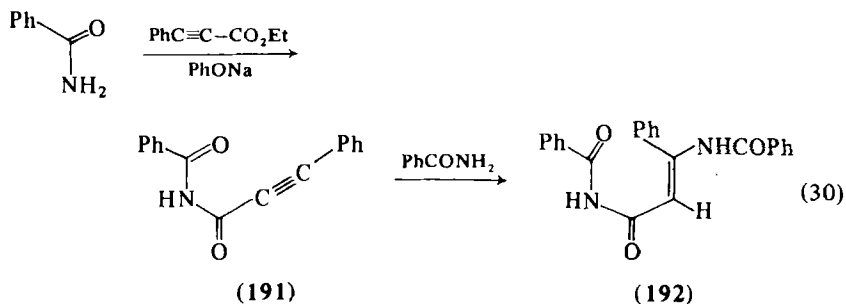
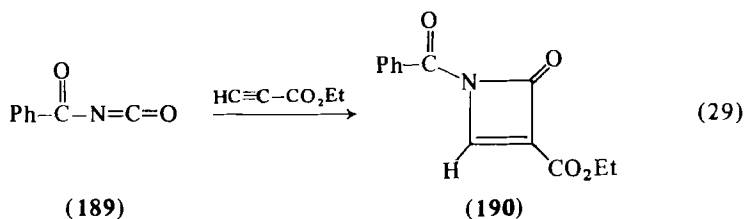


G. AMIDES, IMIDES, AMIDINES, AND GUANIDINES

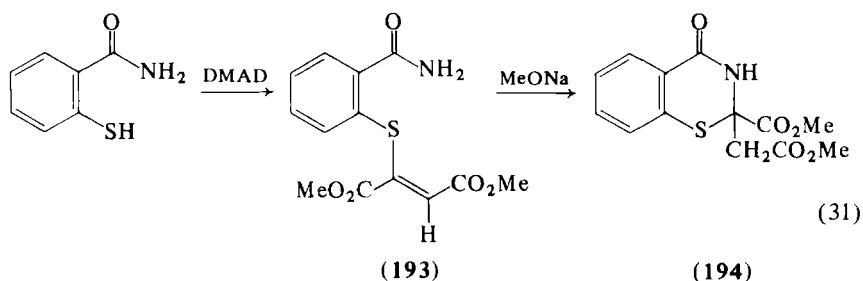
a. *Amides*. Amides react very sluggishly with acetylenic esters. However, reactions can be carried out in the presence of a basic catalyst or under more forcing conditions, employing higher temperatures, or photochemically. Thus, the addition of formamide to DMAD has been reported to proceed under photochemical conditions to give diethyl



SCHEME 29



1,2-dicarbamoylsuccinate.¹³² Likewise, the reaction of benzamide with ethyl phenylpropiolate in the presence of sodium ethoxide has been shown to give a mixture of products consisting of **191** and **192** [Eq. (30)].¹³³ Heindel and co-workers^{47-49,134,135} have studied the reaction of some *ortho*-substituted benzamides with DMAD and have shown that cyclic products are formed in these reactions, arising through a Michael addition of the amide function present in the initially formed adducts. In the reaction of *o*-mercaptobenzamide, for example, the products formed are dimethyl *o*-carboxamidophenylthiofumarate (**193**) and the 1,3-benzothiazin-4-one (**194**) [Eq. (31)].¹³⁵



The reaction of arylacetamides with ethyl phenylpropiolate gives 4,5-diaryl-1,5-dihydro-2*H*,6*H*-pyridine-2,6-diones (**197**).^{136,137} It has been suggested that the pyridinediones in these reactions are formed through the initial addition of either the amide anion (**195**) or the carbanion (**196**), generated under basic conditions, to ethyl phenylpropiolate (Scheme 30).

Shim and Broom¹³⁸ have studied the reaction of 6-aminouracils (**198**) with DMAD and have shown that, in solvents such as dimethylformamide, 1,3-disubstituted-6-amino-5-(3-carbomethoxy-2-propynoyl)uracils (**199**) are formed, whereas in protic solvents like methanol, 2,4,5-trioxo-7-carbomethoxypyrido[2,3-*d*]pyrimidines (**200**) are obtained (Scheme 31). The reaction of 2-pyridone with DMAD gives rise to a mixture of products consisting of a 1 : 1 adduct (**201**), a 2 : 1

¹³² D. Elad, *Proc. Chem. Soc.*, 225 (1962).

¹³³ S. Ruhemann, *J. Chem. Soc.* 95, 984 (1909).

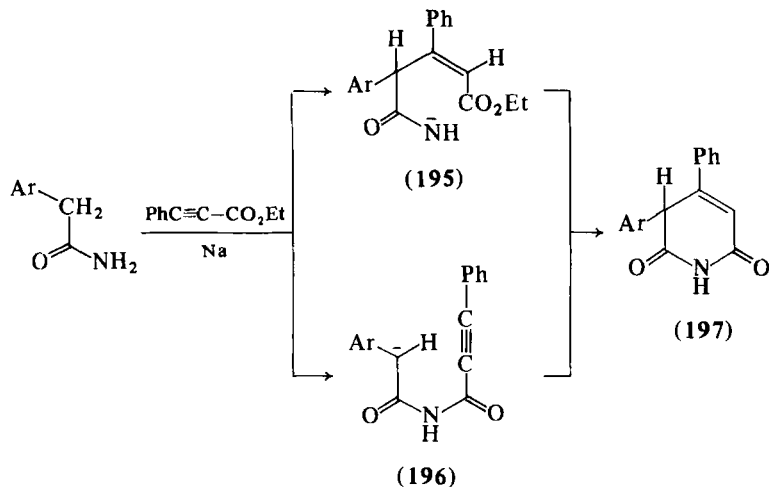
¹³⁴ N. D. Heindel and L. A. Schaeffer, *J. Org. Chem.* 35, 2445 (1970); *J. Med. Chem.* 13, 981 (1970) [CA 73, 87874 (1970)].

¹³⁵ N. D. Heindel and C. C. Ho Ko, *J. Heterocycl. Chem.* 7, 1007 (1970).

¹³⁶ H. N. Al-Jallo, I. E. El-Kholy, M. Y. Shandala, and F. H. Al-Hajjar, *J. Chem. Soc.*, C, 915 (1969).

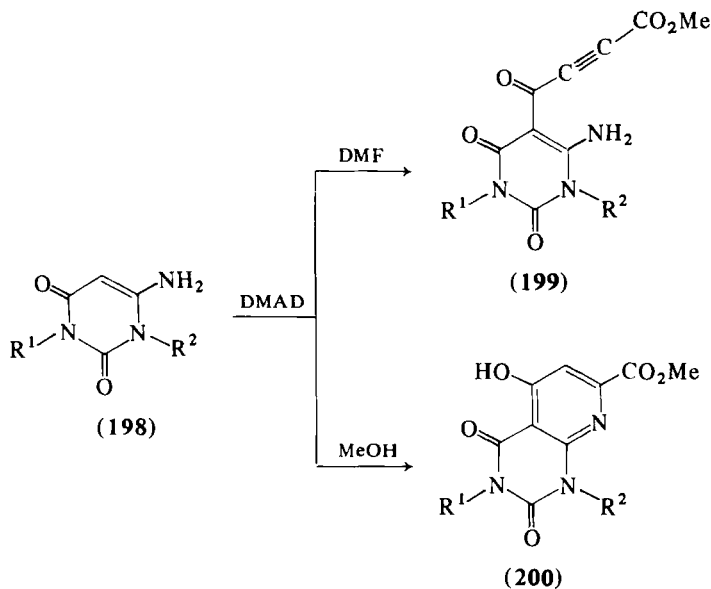
¹³⁷ H. N. Al-Jallo and F. H. Al-Hajjar, *J. Chem. Soc.*, C, 3916 (1971).

¹³⁸ J. L. Shim (with A. D. Broom), Ph.D. Thesis Univ. of Utah (1972); *Diss. Abstr. B* 33, 1063 (1972).



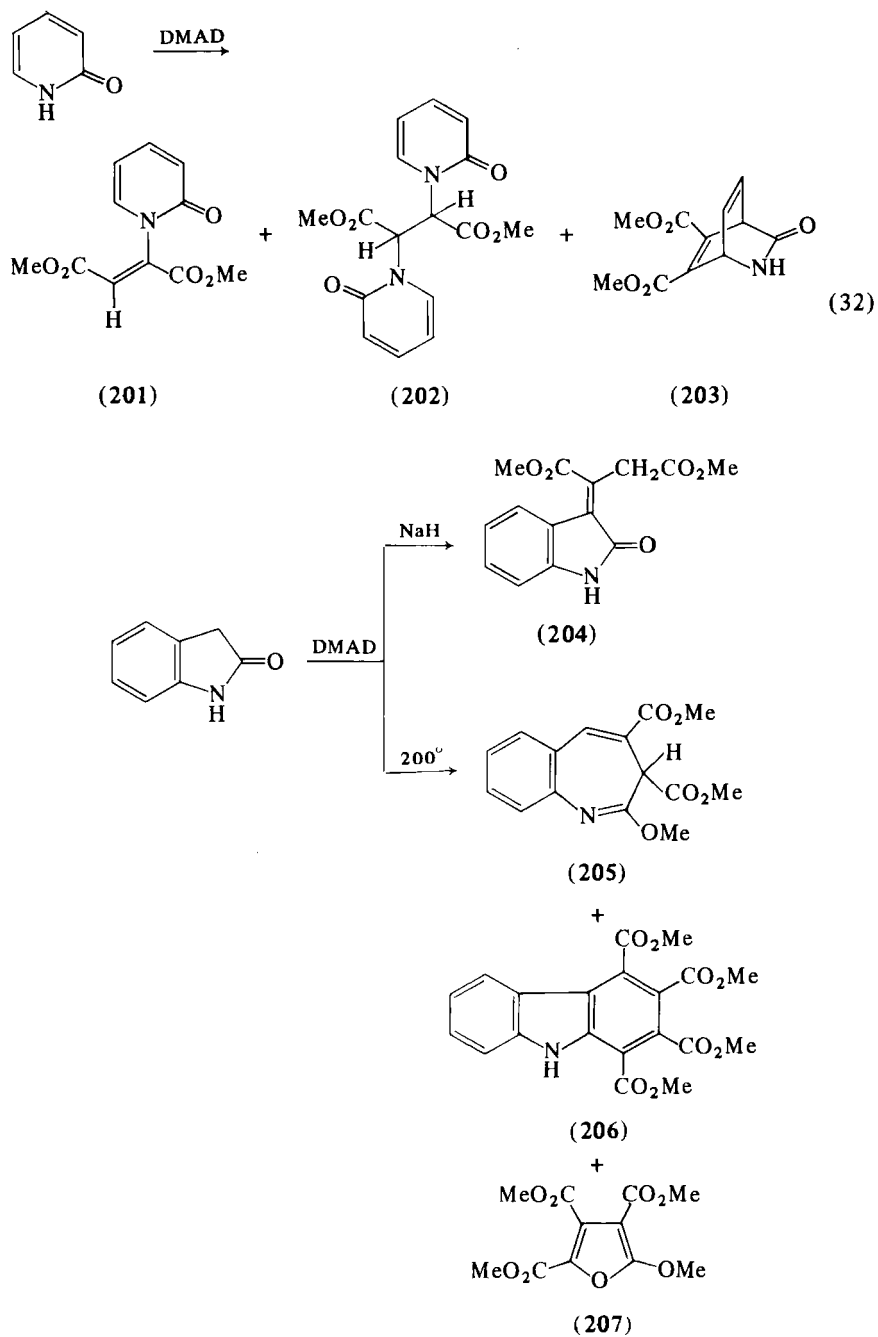
SCHEME 30

adduct (202), and a small amount of the Diels–Alder adduct (203), whereas the reaction of 1-methyl-2-pyridone gives mainly the corresponding Diels–Alder adduct [Eq. (32)].¹³⁹



SCHEME 31

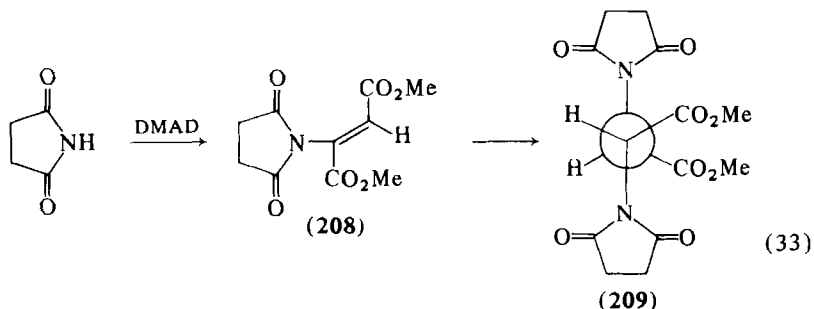
¹³⁹ R. M. Acheson and P. A. Tasker, *J. Chem. Soc., C*, 1542 (1967).



SCHEME 32

Winterfeldt and Nelke⁴⁵ have shown that oxindole reacts with DMAD in presence of sodium hydride to give dimethyl oxindolylidene-3-succinate (**204**). However, when the reaction is carried out in the absence of any base, at around 200°, the products formed are the azepine derivative **205**, the carbazole **206**, and the furan **207** (Scheme 32). Similarly, the reaction of *N*-methyloxindole with DMAD in presence of sodium methoxide gives rise to *N*-methyloxindolylidene-3-succinate.⁴⁵

b. *Imides*. Gudi and George¹⁰⁷ have shown that several products are formed in the reaction of cyclic imides with DMAD. Thus, succinimide with DMAD in presence of potassium carbonate gives a mixture of dimethyl succinimidofumarate (**208**) and dimethyl α,β -



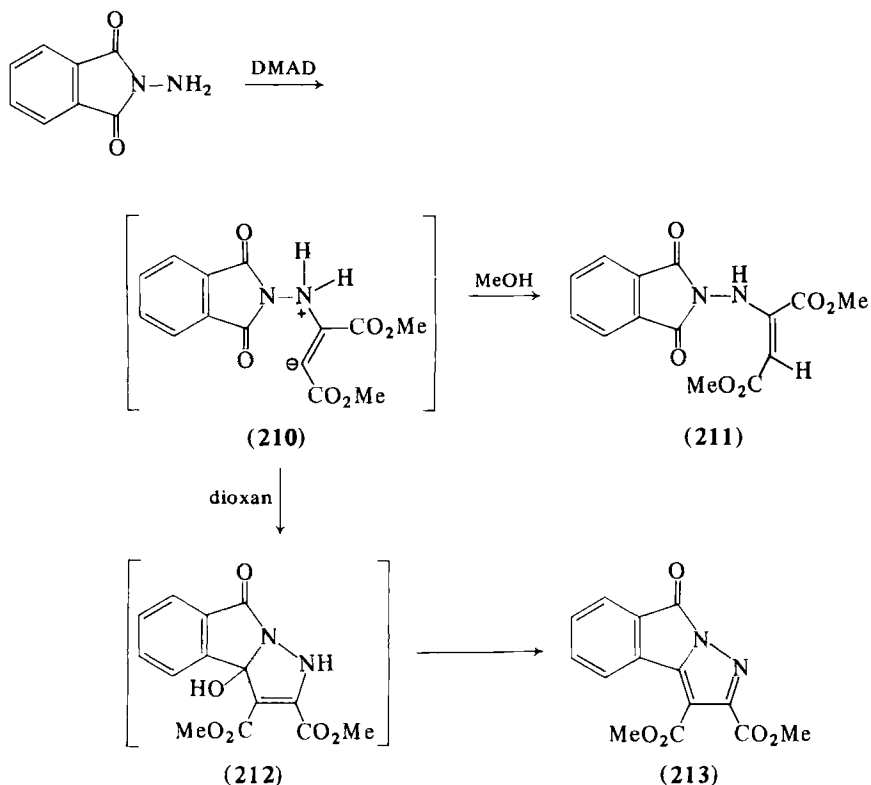
disuccinimidosuccinate (**209**) [Eq. (33)]. Similar reactions have been observed in the case of phthalimide, isatin, and saccharin. The reaction of *N*-aminophthalimide with DMAD gives rise to dimethyl *N*-phthalimidylaminofumarate (**211**) in a protic solvent such as methanol. However, in dioxan medium, the product is the isoindolo[2,1-*b*]pyrazole (**213**). It was suggested that **213** is formed through intramolecular cyclization of the zwitterionic intermediate **212** (Scheme 33).

c. *Amidines*. Ruhemann and Stapleton¹⁴⁰ have studied the reaction of benzamidine with ethyl phenylpropiolate and have shown that at room temperature the product formed is the glyoxalidone **214**, whereas at higher temperatures a mixture of **214** and the dihydropyrimidone **215** is formed [Eq. (34)]. Similarly, benzalbenzamidine (**216**) gives the dihydropyrimidine derivative (**217**) [Eq. (35)].¹⁴¹ Viehe and Fuks¹⁴² have studied the reaction of the trisubstituted amidine **218a** with DMAD and have

¹⁴⁰ S. Ruhemann and H. E. Stapleton, *J. Chem. Soc.* 77, 239 (1900).

¹⁴¹ V. M. Cherkasov, N. A. Kapron, and V. N. Zavatskii, *Ukr. Khim. Zh.* 35, 1057 (1969) [*CA* 72, 43596 (1970)].

¹⁴² H. G. Viehe and R. Fuks, unpublished results; see Fuks and Viehe.⁶



SCHEME 33

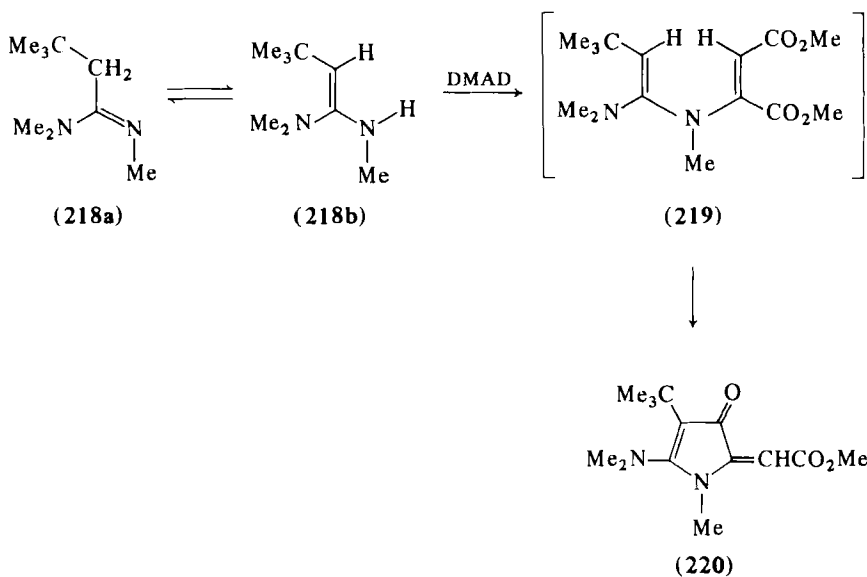
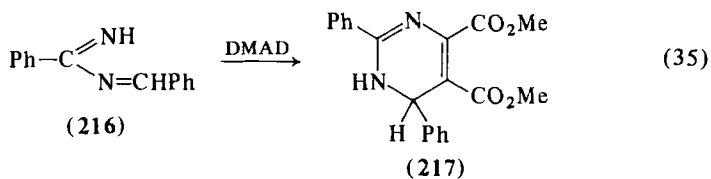
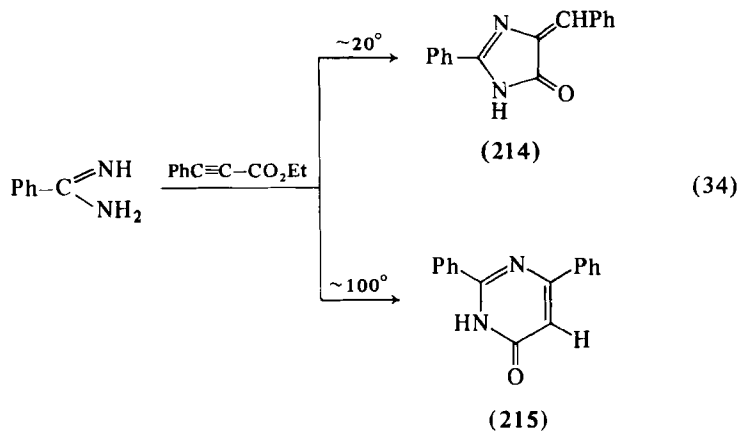
observed that the dihydropyrrole derivative (220) is formed. The formation of 220 may proceed through the enamine intermediate 219 (Scheme 34).

d. *Guanidines*. Imidazolidine derivatives have been reported in the reaction of urea and of guanidine with ethyl phenylpropiolate.¹⁴⁰ Ruhemann and Stapleton¹⁴³ have reported the formation of the pyrimidin-4-one 224a in the reaction of guanidine 221a with DMAD. However, a reinvestigation by Sasaki and co-workers¹⁴⁴ has shown that the guanidines 221a and 221b on treatment with DMAD, give the imidazolidine derivatives 222a and 223a (Scheme 35). Similarly, Katner and Ziege¹⁴⁵ have recently found that the reactions of guanidine (221a)

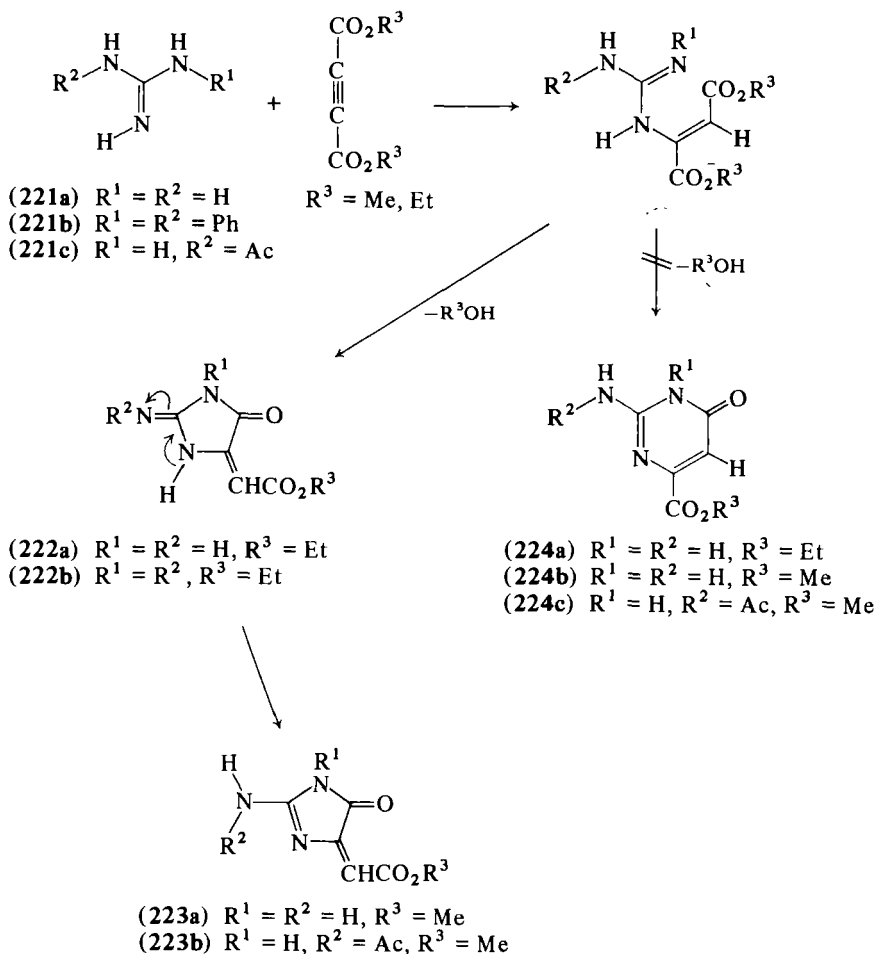
¹⁴³ S. Ruhemann and H. E. Stapleton *J. Chem. Soc.* 77, 804 (1900).

¹⁴⁴ H. Sasaki, H. Sakata, and Y. Iwanami, *Nippon Kagaku Zasshi* 85, 704 (1964) [*CA* 62, 14678 (1965)].

¹⁴⁵ A. S. Katner and E. A. Ziege, *Chem. Commun.*, 864 (1971).



SCHEME 34

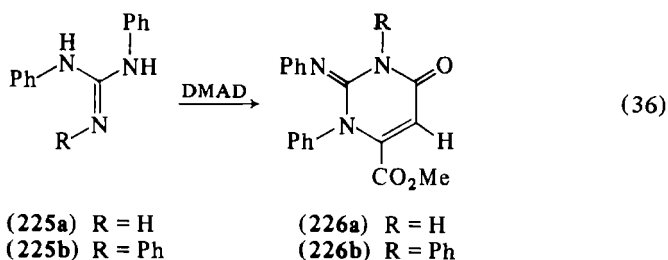


SCHEME 35

and acetylguanidine (221c) with DMAD give the imidazoline derivatives 223a and 223b, respectively. These imidazoline derivatives were earlier formulated as the pyrimidines 224a and 224c (Scheme 35).¹⁴⁶ Lown and Ma^{106,147} have reported pyrimidones (226) from the reaction of 1,3-diphenylguanidine (225a) and triphenylguanidine (225b) with DMAD [Eq. 36]. The reaction of semicarbazide with diethyl acetylenedicarboxylate, on the other hand, yields diethyl oxaloacetate semicarbazone.¹⁴⁴ Semicarbazidimine, however, gives a triazine derivative.¹⁴⁴

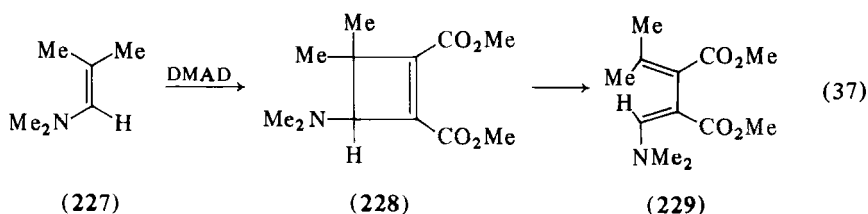
¹⁴⁶ J. F. W. Keana, F. P. Mason, and J. S. Bland, *J. Org. Chem.* **34**, 3705 (1969).

¹⁴⁷ J. W. Lown and J. C. N. Ma, *Can. J. Chem.* **45**, 939 (1967).



H. ENAMINES

Several reactions of enamines with acetylenic esters are reported.¹⁴⁸⁻¹⁵⁰ In general, [2 + 2] mode of addition leads to cyclobutene intermediates, which undergo ring opening, yielding dienamines. *N,N*-Dimethylisobutenylamine (227) with DMAD, for example, gives the dienamine



229 [Eq. (37)].¹⁴⁸ An interesting case of the reaction of an enamine is found in the reaction of 1-ethyl-2-methyleneaziridine with DMAD, giving trimethyl 1-ethylpyrrole 2,3,4-tricarboxylate (233). It has been suggested that this reaction may proceed through intermediates like 231 and 232 (Scheme 36).¹⁵¹ The reaction of cyclic enamines, on the other hand, gives rise to ring-enlarged, cyclic dienamines. Thus, in the reaction of cyclohexenylamines (234) with DMAD, the cyclooctadienylamines (236) are formed, probably through the bicyclooctene intermediate (235) (Scheme 37).¹⁴⁹ Similar reactions have been observed in the case of five-, seven-, eight-, and twelve-membered ring enamines, on treatment with DMAD¹⁴⁸ or methyl propiolate.¹⁵² The reaction of cyclohexenylamines

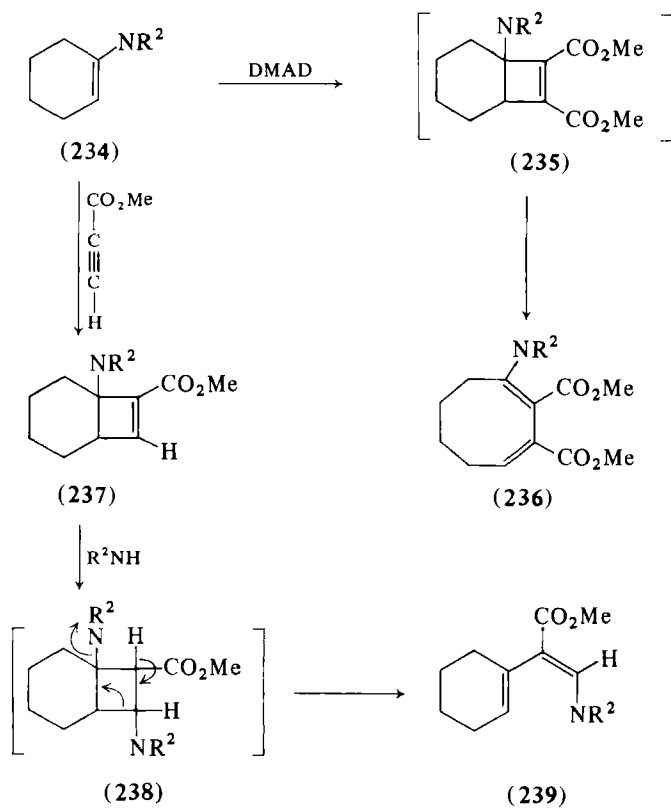
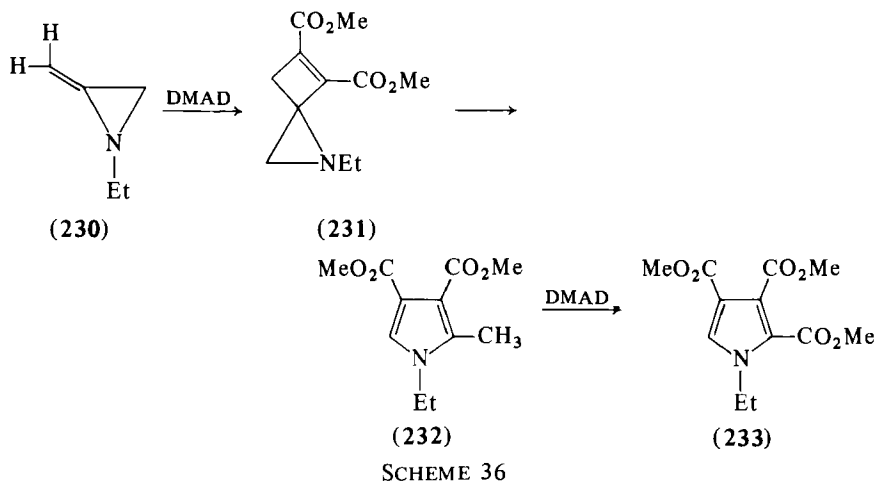
¹⁴⁸ K. C. Brannock, R. D. Burpitt, V. W. Goodlett, and J. G. Thweatt, *J. Org. Chem.* **28**, 1464 (1963).

¹⁴⁹ C. F. Huebner, L. Dorfman, M. M. Robison, E. Donoghue, W. G. Pierson, and P. Strachan, *J. Org. Chem.* **28**, 3134 (1963).

¹⁵⁰ G. A. Berchtold and G. F. Uhlig, *J. Org. Chem.* **28**, 1459 (1963).

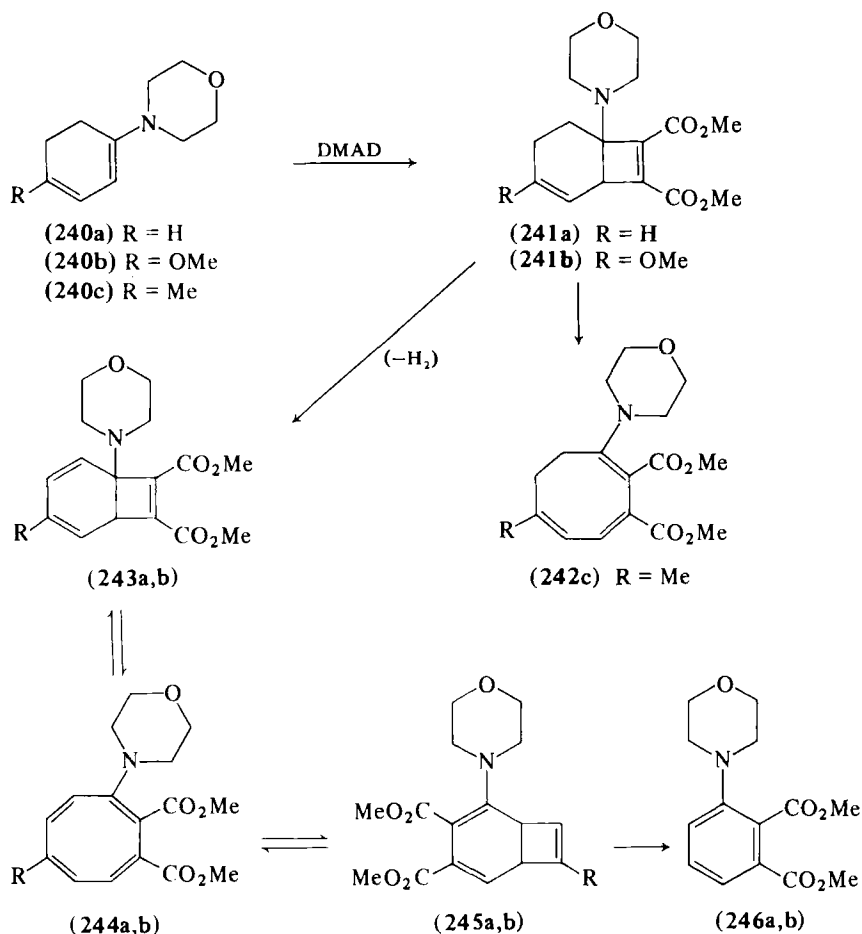
¹⁵¹ R. C. Cookson, B. Halton, I. D. R. Stevens, and C. T. Watts, *J. Chem. Soc., C*, 928 (1967).

¹⁵² K. C. Brannock, R. D. Burpitt, V. W. Goodlett, and J. G. Thweatt, *J. Org. Chem.* **29**, 818 (1964).



(234) with methyl propiolate is of interest in that aminoacrylates (239) are formed in these cases. It has been suggested that the formation of 239 may be explained in terms of the addition of a secondary amine to the initially formed intermediate 237 to give 238, which then loses the amine moiety, accompanied by ring opening (Scheme 37).¹⁵² Bose and co-workers¹⁵³ have successfully utilized the ring-enlargement reaction of enamine adducts in the synthesis of bishomosteroids.

Birch and Hutchinson¹⁵⁴ have reported some of the addition reactions of cyclohexadienylamines with DMAD and have shown that the stability of the bicyclooctadienes formed in these reactions depends to a



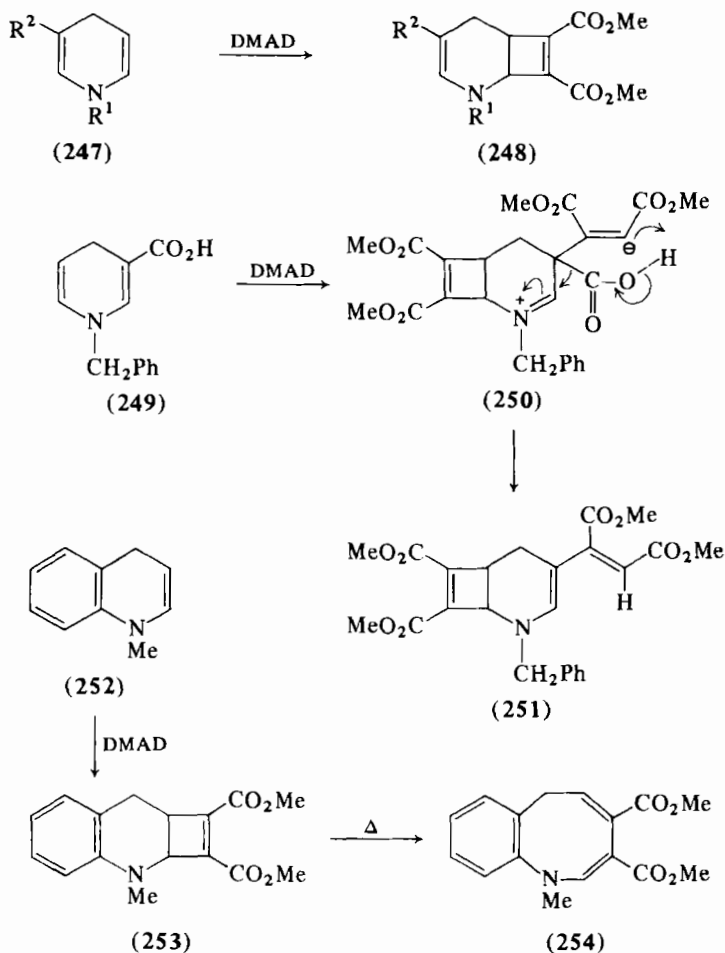
SCHEME 38

¹⁵³ A. K. Bose, G. Mina, M. S. Manhas, and E. Ruzicidlo, *Tetrahedron Lett.*, 1467 (1963).

¹⁵⁴ A. J. Birch and E. G. Hutchinson, *J. Chem. Soc., C*, 3671 (1971).

large extent on the nature of the substituent present in the 4-position of the cyclohexadienyl unit. Thus, *N*-(cyclohexa-1,3-dienyl)morpholine (**240a**) gives dimethyl 6-morpholinobicyclo[4.2.0]octa-2,7-diene-7,8-dicarboxylate (**241a**). Interestingly, **241a** on dehydrogenation gives dimethyl 3-morpholinophthalate (**246**) (Scheme 38). Similarly, the reaction of **240b**, containing a 4-methoxy group, gives rise to the corresponding bicyclooctadiene derivative (**241b**). However, the diene **240c**, containing a 4-methyl substituent, gives the ring-enlarged product, namely, the cyclooctatriene (**242c**) (Scheme 38).

Acheson and co-workers^{155,156} have recently shown that the reaction

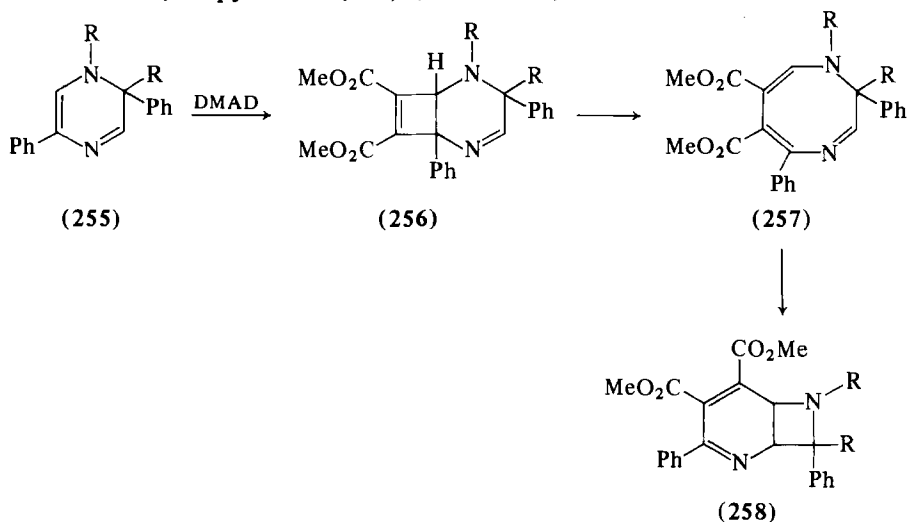


SCHEME 39

¹⁵⁵ R. M. Acheson and N. D. Wright, *Chem. Commun.*, 1421 (1971).

¹⁵⁶ R. M. Acheson, N. D. Wright, and P. A. Tasker, *J. Chem. Soc., Perkin Trans. I*, 2918 (1972).

of 1-alkyl-1,4-dihydropyridines (247) with DMAD yields 1,4,4a,6a-tetrahydrocyclobuta[*b*]pyridines (248). These cyclobutenes have been found to be thermally stable, and they do not undergo facile ring-enlargement. On the other hand, the reaction of 1-benzyl-3-carboxyl-1,4-dihydropyridine (249) with DMAD gives 251 by the elimination of CO₂ from the initial adduct (250) (Scheme 39). A similar observation has been made in the reaction of 1-benzyl-3-carbamoyl-1,4-dihydropyridine with DMAD.¹⁵⁶ It is interesting to note that in the reaction of 1-methyl-1,4-dihydroquinoline (252) with DMAD, the initially formed cycloadduct (253) undergoes valence isomerization to 3,4-dicarbomethoxy-1-methyl-1,6-dihydro-1-benzazocine (254).¹⁵⁷ Similarly, the reaction of 1,2-dihydropyrazines (255) leads to 3,8-dihydro-azetidino[3,2-*b*]pyridines (258) (Scheme 40).¹⁵⁸



SCHEME 40

Benzazepine derivatives (261) are formed in the reaction of 1-acetyl-3-piperidinoindole (259) with DMAD and methyl propiolate (Scheme 41).¹⁵⁹ A similar reaction has been observed in the case of 2-ethoxyindole, on treatment with DMAD.¹⁶⁰

Acheson and co-workers¹⁶¹ have shown that 1-methylindole reacts with DMAD in acetonitrile, yielding dimethyl 1-methylbenz[*b*]azepine-

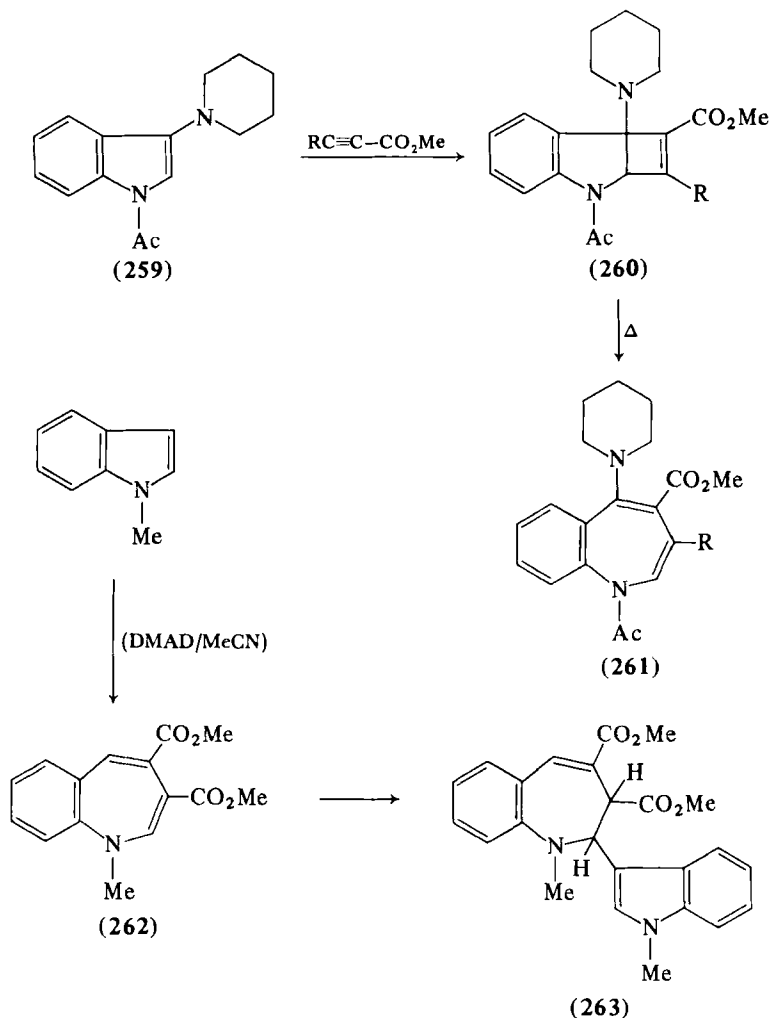
¹⁵⁷ P. G. Lehman, *Tetrahedron Lett.*, 4863 (1972).

¹⁵⁸ J. W. Lown and M. H. Akhtar, *Tetrahedron Lett.*, 3727 (1973).

¹⁵⁹ M. S. Lin and V. Snieckus, *J. Org. Chem.* **36**, 645 (1971).

¹⁶⁰ H. Plieninger and D. Wild, *Chem. Ber.* **99**, (1966).

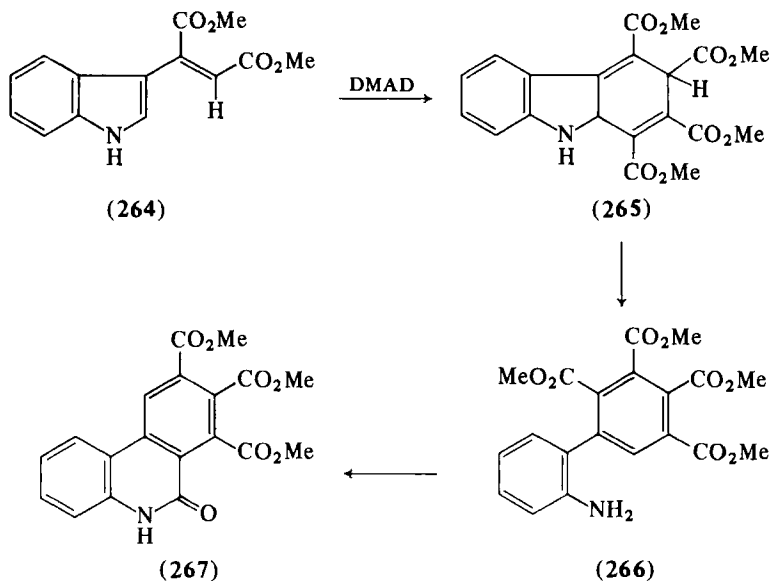
¹⁶¹ R. M. Acheson, J. N. Bridson, and T. S. Cameron, *J. Chem. Soc., Perkin Trans. I*, 968 (1972).



SCHEME 41

3,4-dicarboxylate (262). Further reaction of 1-methylindole with 262 gives dimethyl 2,3-dihydro-1-methyl-2-(1-methylindol-3-yl)benz[*b*]-azepine-3,4-dicarboxylate (263) (Scheme 41).¹⁶¹ Treatment of indole with DMAD, likewise gives the corresponding 2,3-dihydro-2-(indol-3-yl)benzazepine derivative. 1,3-Dimethylindole, on the other hand, reacts with DMAD in presence of $BF_3 \cdot Et_2O$ to give a mixture of products consisting of the corresponding benzazepine derivative and also the indolyl maleate and fumarate.¹⁶²

¹⁶² F. Fried, J. B. Taylor, and R. Westwood, *Chem. Commun.*, 1226 (1971).



SCHEME 42

A vinylogous indole derivative like **264** reacts with DMAD to give a phenanthridone derivative (**267**) (Scheme 42).¹⁶³ An interesting case of the reaction of an enamine system is observed in the case of the 3*H*-pyrrolizine (**268**), which gives a mixture of the azepino[2,1,7-*cd*]pyrrolizine derivative (**271**) and the 1:1 adduct (275) (Scheme 43).^{164,165} The reaction of 3-ethoxycarbonylmethylene-3*H*-pyrrolizine, on the other hand, yields a pyrrolo[2,1,5-*cd*]indolizine derivative.¹⁶⁵ The reaction of indolizines (**276**) with DMAD gives rise to quinolizines (**281**). At room temperature, the primary adduct (**278**) is isolated and undergoes thermal cyclization to **281** (Scheme 44).¹⁶⁶

The reaction of 1-methyl-2-(methylmercapto)-2-pyrroline (**282**) with DMAD is known to give a dihydroazepine derivative (**283**) [Eq. (38)].¹⁶⁷ The recent report of the reaction of 1-methyl-2-pyrrolidone dimethyl-acetal (**284**) with DMAD to give products like **286**, **287**, **288**, and **289** may be interpreted as essentially the reaction of the enamine system (**285**) (Scheme 45).¹⁶⁷ Other examples of the reaction of enamines include the reaction of the pyrrolidinopentenone (**290**) to give the phthalate (**293**)

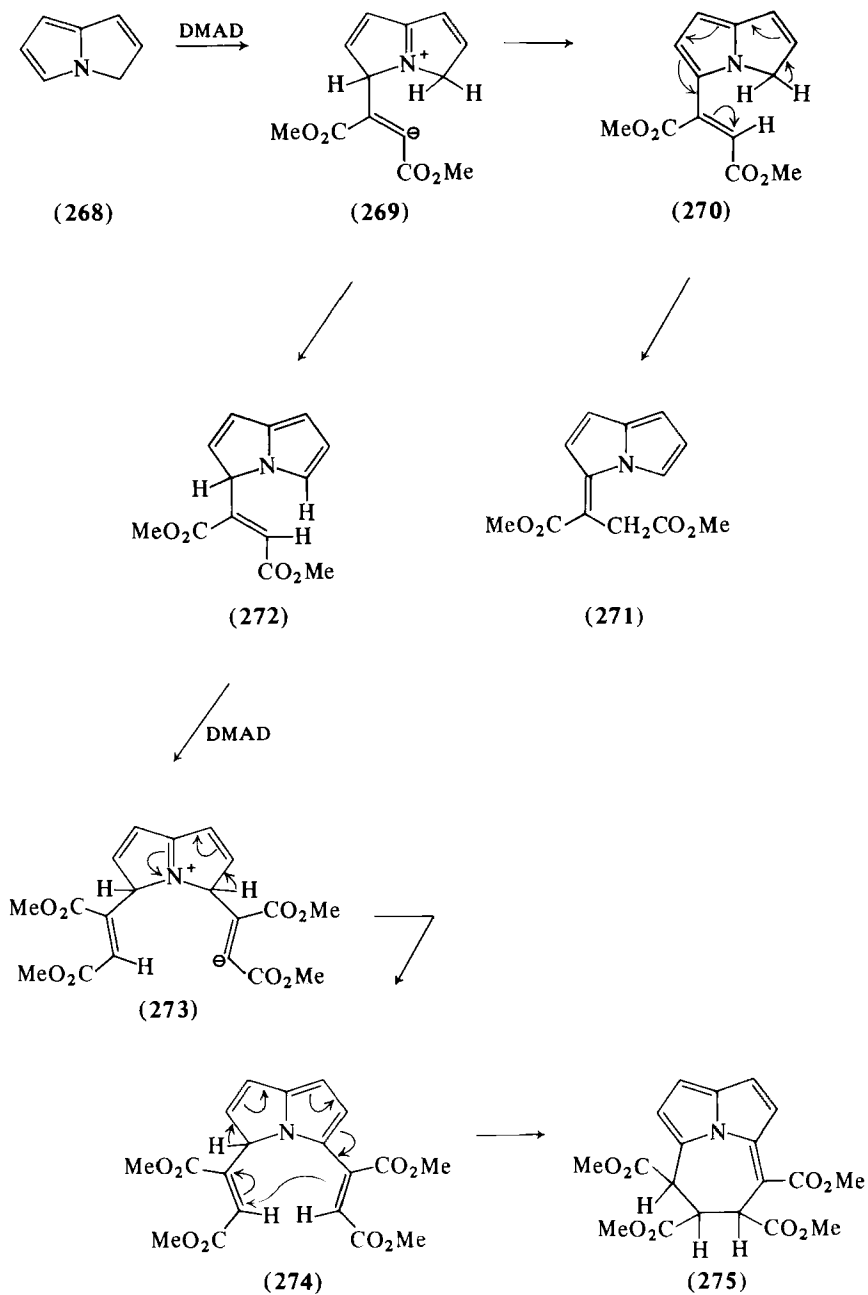
¹⁶³ R. A. Johnson, Ph.D. Thesis, Univ. of Minnesota (1965); *Diss. Abstr. B* 26, 5719 (1966).

¹⁶⁴ D. Johnson and G. Jones, *J. Chem. Soc., Perkin Trans. I*, 840 (1972).

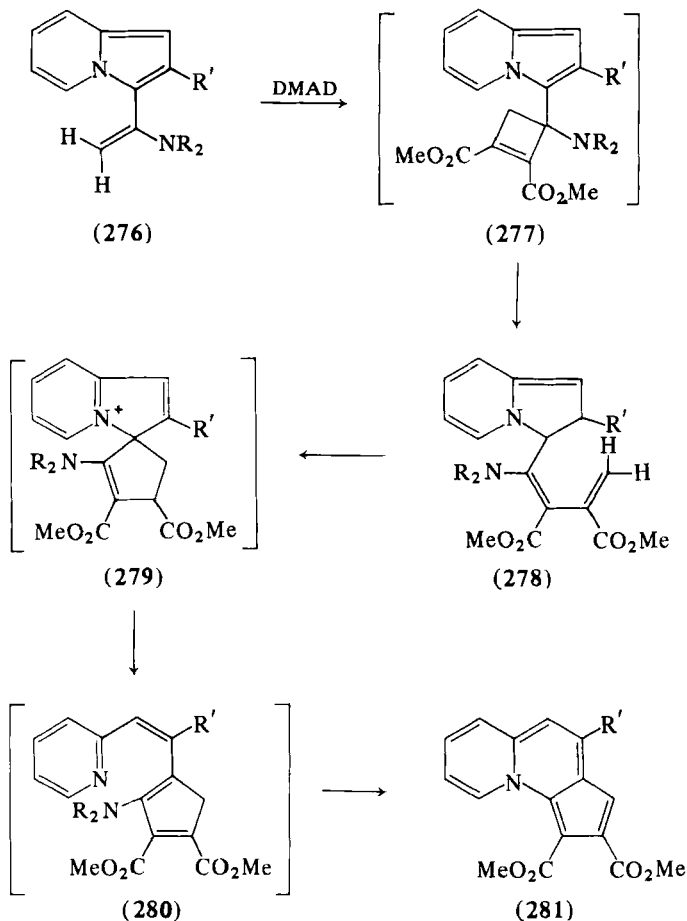
¹⁶⁵ D. Johnson and G. Jones, *J. Chem. Soc., Perkin Trans. I*, 844 (1972).

¹⁶⁶ W. K. Gibson and D. Leaver, *J. Chem. Soc., C*, 324 (1966).

¹⁶⁷ T. Oishi, S. Murakami, and Y. Ban, *Chem. Pharm. Bull.* 20, 1740 (1972) [CA 77, 126351 (1972)].

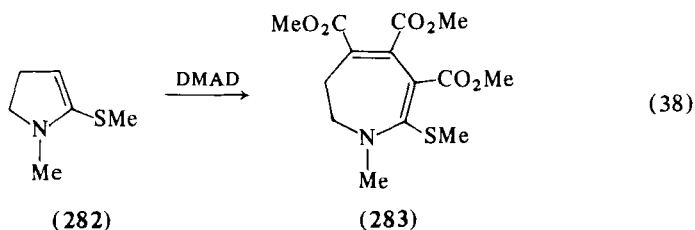


SCHEME 43

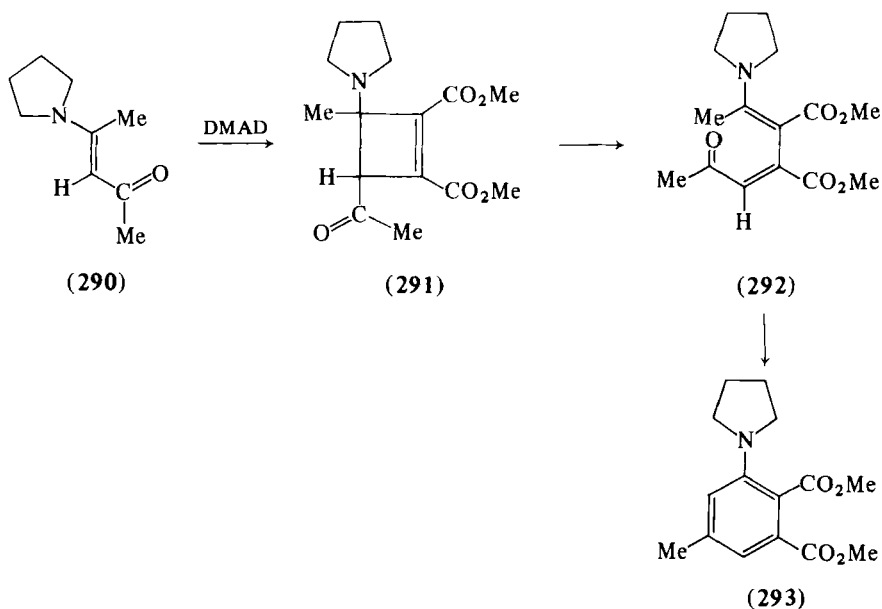
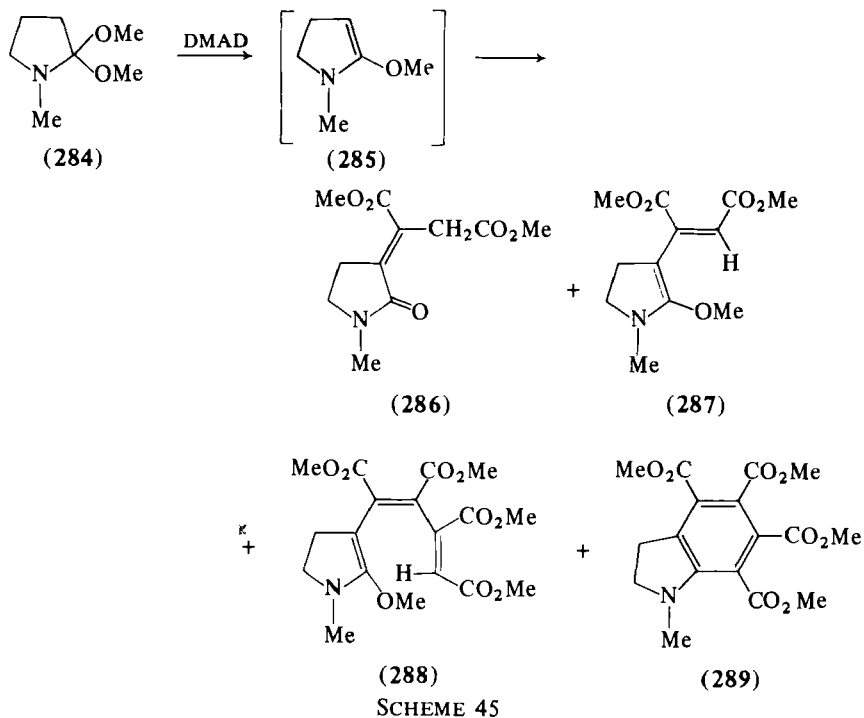


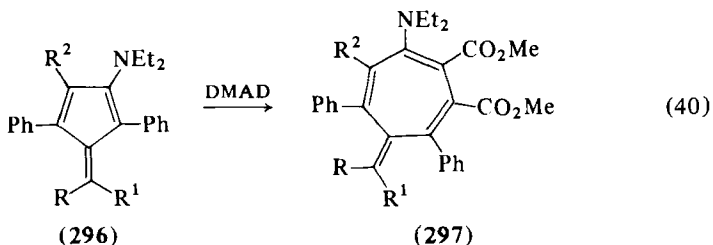
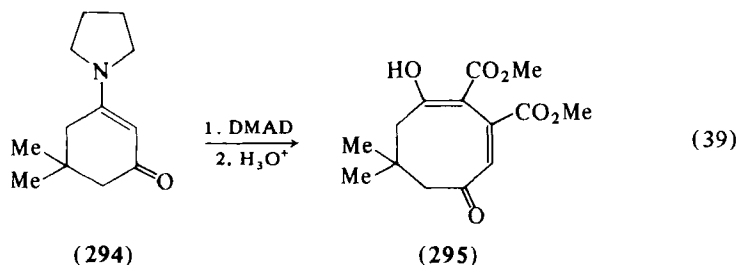
SCHEME 44

(Scheme 46),¹⁴⁹ of 5,5-dimethyl-1-pyrrolidinocyclohex-1-en-3-one (294) to give the cyclooctadienone (295) [Eq. (39)],¹⁴⁹ and of 3-aminofulvenes (296) to give the heptafulvenes (297) [Eq. (40)].¹⁶⁸

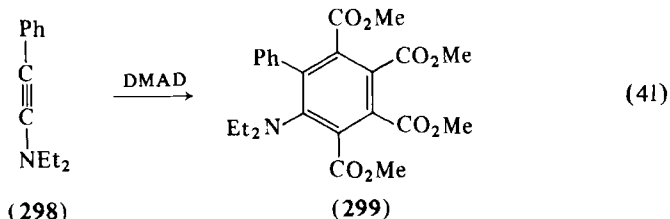


¹⁶⁸ T. Eicher and T. Pfister, *Tetrahedron Lett.*, 3969 (1972).





The reaction of alkynylamines with acetylenic esters give benzene derivatives.^{169,170} Thus, in the reaction of phenyl diethylaminoacetylene (298) with DMAD, tetramethyl 1-diethylamino-2-phenyl-3,4,5,6-tetracarboxylate (299) is formed [Eq. (41)].¹⁶⁹



III. Oxygen-Containing Nucleophiles

A. ALCOHOLS AND PHENOLS

Moureu^{171,172} investigated the addition of alcohols, catalyzed by sodium methoxide, to acetylenic esters and has shown that enol ethers are formed as primary adducts. It has been shown that compounds such as potassium cyanide,¹⁷³ a mixture of mercuric oxide, boron trifluoride,

¹⁶⁹ H. G. Viehe, R. Fuks, and M. Reinstein, *Angew. Chem., Int. Ed. Engl.* **3**, 581 (1964).

¹⁷⁰ J. Ficini and C. Barbara, *Bull. Soc. Chim. Fr.*, 871 (1964) [*CA* **61**, 2991 (1964)].

¹⁷¹ C. Moureu, *C. R. Acad. Sci.* **137**, 259 (1903); *Brit. Chem. Abstr.* **84**, 698 (1903).

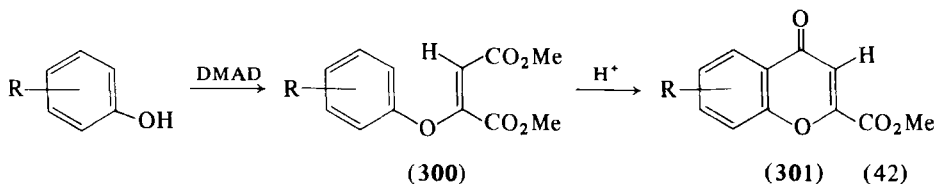
¹⁷² C. Moureu, *C. R. Acad. Sci.* **138**, 206 (1904); *Brit. Chem. Abstr.* **86**, 286 (1904).

¹⁷³ A. Michael and N. Weiner, *J. Amer. Chem. Soc.* **59**, 744 (1937).

nd trichloroacetic acid,¹⁷⁴⁻¹⁷⁶ anhydrous copper sulfate,¹⁷⁷ alkoxides,^{171,172,178} and tertiary amines^{61,80,178} catalyze the addition of alcohols to acetylenic esters. The geometry of the addition products depends upon the catalyst and reaction conditions. Thus, alcohols add thermally to acetylenic esters (200°), to give primarily the alkoxy-maleates,⁶¹ whereas, under the influence of catalysts, the alkoxy-fumarates are formed in larger amounts.^{61,179} Kinetic studies by Mueller¹⁷⁸ have shown that, in the base-catalyzed addition of alcohols to acetylenic esters, the rate-determining step involves the concentration terms of the alcohol, the acetylenic ester, and the added base.

The reaction of few phenols with acetylenic esters is reported in the literature.^{61,180-189} George and co-workers,¹⁸⁹ on the basis of detailed nuclear magnetic resonance (NMR) studies of the product mixtures formed in the reaction of several phenols with DMAD, have concluded that, as the size of the attacking nucleophile increases, there is a greater tendency for the formation of maleates, which are sterically more favored as compared to the fumarates.

The 1:1 adducts (300) formed in the reaction of phenols with DMAD have been successfully employed in the synthesis of several chromone derivatives (301) [Eq. (42)].^{183,185,186,188,190} An interesting case



¹⁷⁴ L. J. Haynes, E. R. H. Jones, and M. C. Whiting, *Chem. Ind. (London)*, 423 (1946).

¹⁷⁵ R. A. Raphael, *J. Chem. Soc.*, 805 (1947).

¹⁷⁶ A. O. Zoss and G. F. Hannion, *J. Amer. Chem. Soc.* **63**, 1151 (1941).

¹⁷⁷ F. Straus and W. Voss, *Ber.* **59**, 1681 (1926).

¹⁷⁸ W. J. Mueller, Ph.D. Thesis, Univ. of Idaho (1970); *Diss. Abstr. B* **31**, 3928 (1971).

¹⁷⁹ E. Winterfeldt, W. Krohn, and H. Preuss, *Chem. Ber.* **99**, 2572 (1966).

¹⁸⁰ R. M. Acheson and J. McK. Woolard, *J. Chem. Soc., C*, 3296 (1971).

¹⁸¹ S. Ruhemann and F. Beddow, *J. Chem. Soc.* **77**, 984 (1900).

¹⁸² S. Ruhemann and F. Beddow, *J. Chem. Soc.* **77**, 1119 (1900).

¹⁸³ S. Ruhemann and H. E. Stapleton, *J. Chem. Soc.* **77**, 1179 (1900).

¹⁸⁴ S. Ruhemann, *J. Chem. Soc.* **83**, 1130 (1903).

¹⁸⁵ S. Ruhemann, *Ber.* **46**, 2188 (1913).

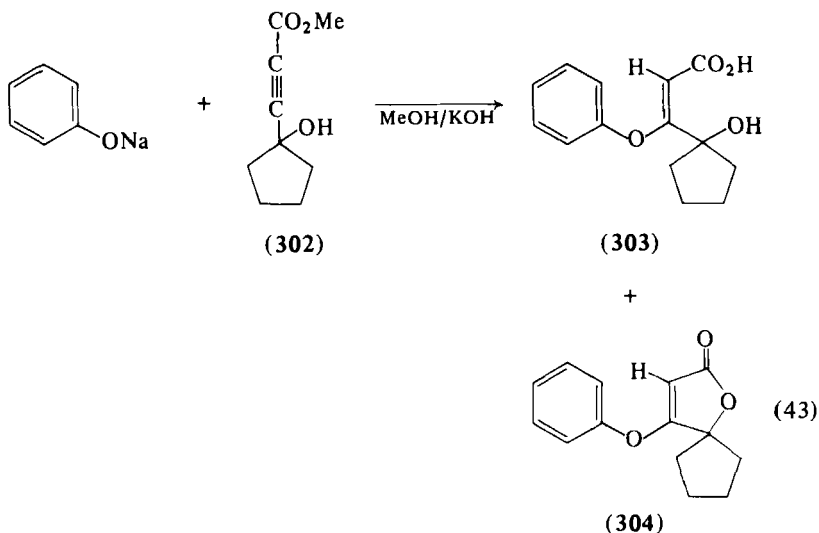
¹⁸⁶ S. Ruhemann, *Ber.* **47**, 119 (1914).

¹⁸⁷ M. T. Bogert and J. K. Marcus, *J. Amer. Chem. Soc.* **41**, 83 (1919).

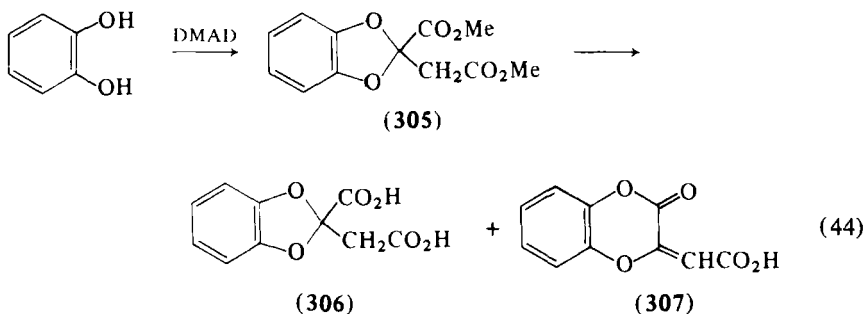
¹⁸⁸ E. Gottesmann, *Ber.* **66**, 1168 (1933).

¹⁸⁹ M. N. Gudi, J. G. Hiriyakkanavar, and M. V. George, *Indian J. Chem.* **7**, 971 (1969).

¹⁹⁰ H. Cairns, A. Chambers, and T. B. Lee, German Patent, 2,142,526 (1972) [*CA* **77**, 34338 (1972)].



of a lactone (304) formation has been observed in the reaction of sodium phenolate with methyl β -(1-hydroxycyclopentyl) propiolate (302), presumably formed through the intermediate 303 [Eq. (43)].¹⁹¹ A similar lactone formation has been observed in the reaction of the corresponding 1-hydroxycyclohexenylpropiolate.¹⁹¹ A benzo-1,3-dioxole



derivative (305) is formed in the reaction of catechol with DMAD.^{192,193} Alkaline hydrolysis of 305 gives rise to the corresponding dicarboxylic acid (306) and a rearranged product (307) [Eq. (44)].¹⁹²

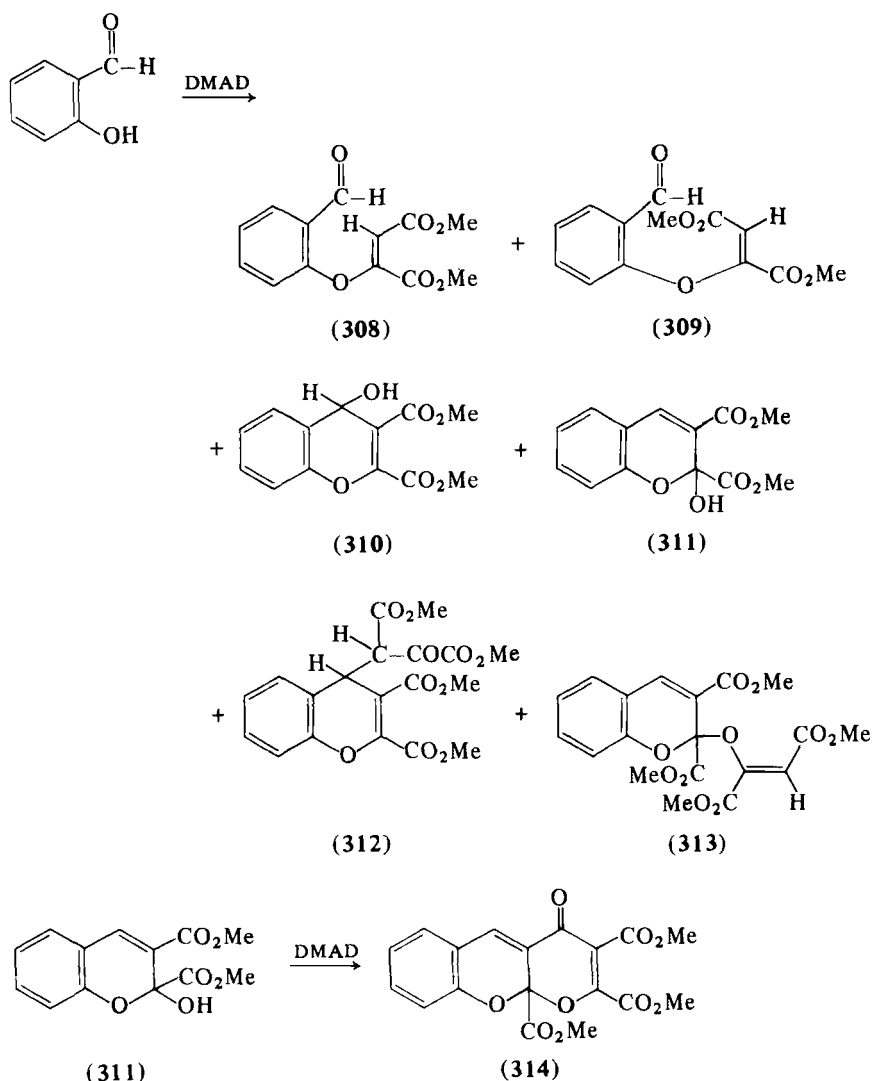
¹⁹¹ V. F. Fuchero, A. I. Kuznetsova, M. V. Mavrov, and E. F. Alekseeva, *Izv. Akad. Nauk SSSR, Otd. Khim. Nauk* 484 (1962) [CA 57, 16382 (1962)].

¹⁹² K. Nagarajan, V. R. Rao, and R. K. Shah, *Indian J. Chem.* 9, 532 (1971).

¹⁹³ V. Rosuati, F. Sanniccolo, and G. Zechhi, *Gazz. Chim. Ital.* 100, 3 (1970) [CA 72, 121407 (1970)].

B. *O*-HYDROXY KETONES

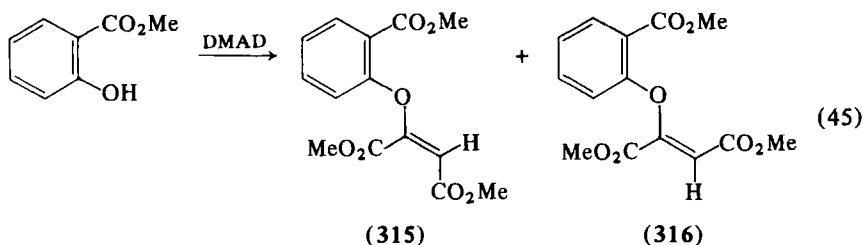
o-Hydroxybenzaldehydes react with DMAD, giving rise to a variety of products. Thus, salicylaldehyde gives a mixture of products consisting of dimethyl *o*-formylphenoxy maleate (308), dimethyl *o*-formylphenoxy fumarate (309), 2,3-dicarbomethoxychrom-2-en-4-ol (310), 2,3-dicarbomethoxychrom-3-en-2-ol (311), dimethyl (2,3-dicarbo-



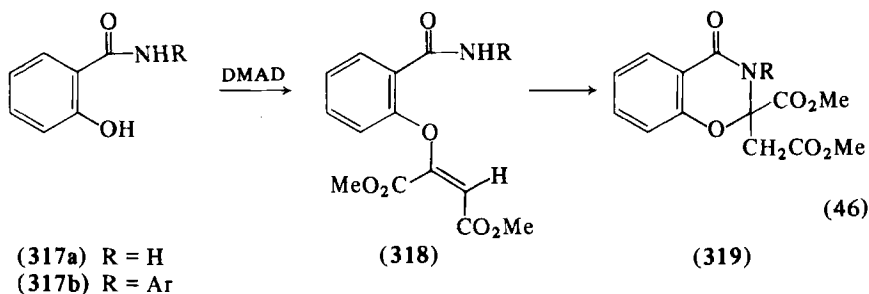
SCHEME 47

methoxychrom-2-en-4-yl) oxaloacetate (312), and dimethyl (2,3-dicarbo-methoxychrom-3-en)-2-oxyfumarate (313). Further reaction of 311 with DMAD results in the formation of 2,3,10a-tricarbo-methoxy-4*H*,10a*H*-benzo[*b*]pyrano[2,3-*b*]pyran-4-one (314) (Scheme 47).¹⁹⁴

The reaction of methyl salicylate with DMAD in presence of triethylamine yields a mixture of *o*-carbo-methoxyphenoxymaleate (315) and fumarate (316) [Eq. (45)].¹³⁴ Similarly, salicylamide (317a) and



salicylanilides (317b) react with DMAD, giving rise to the corresponding 1 : 1 adducts (318), which are cyclized to benzoxazines (319), on treatment with base [Eq. (46)].¹³⁴ A mixture of the 1 : 1 ad-

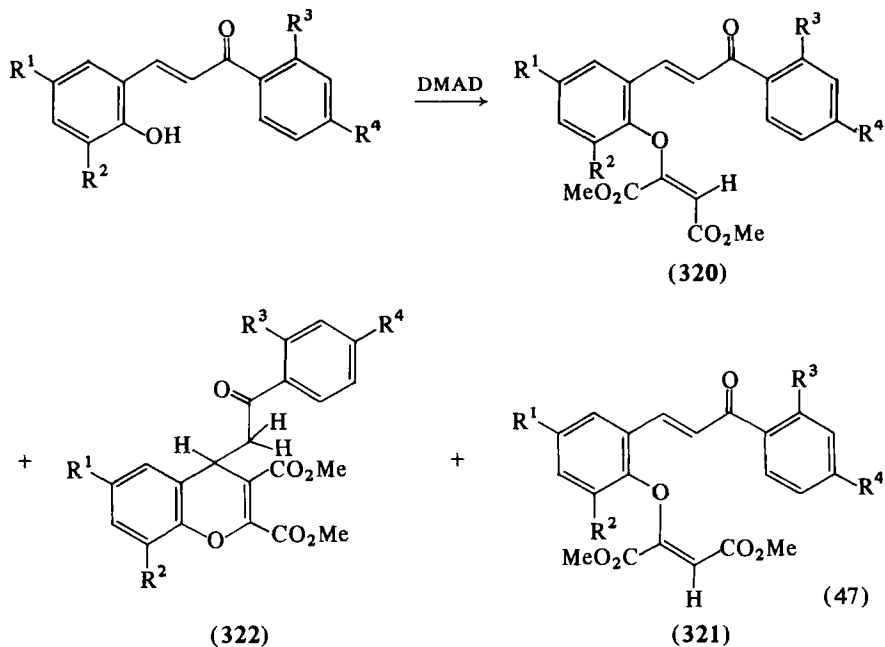


ducts consisting of maleates (320) and fumarates (321) has been reported in the reaction of 2-hydroxychalcones with DMAD [Eq. (47)].¹⁹⁵ The reaction of 2,2'-dihydroxychalcones with DMAD, on the other hand, gives chrom-2-ene derivatives (322), in addition to the corresponding phenoxyfumarates and phenoxy-maleates [Eq. (47)].¹⁹⁵

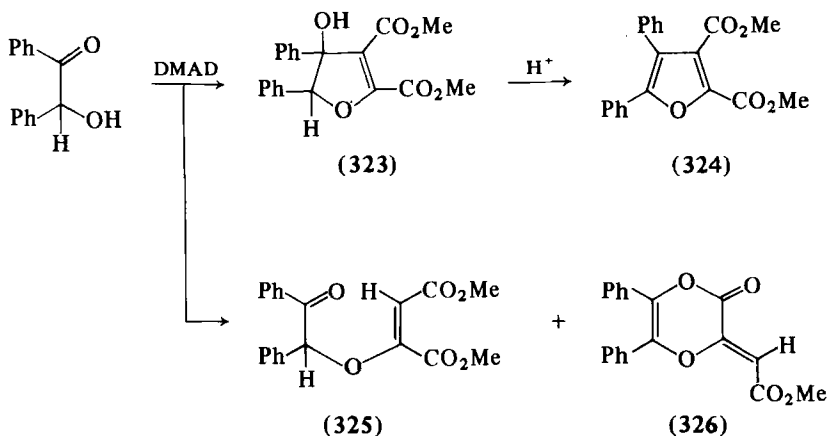
Earlier, it had been reported that the reaction of benzoin with DMAD gives dimethyl 4,5-diphenyl-4-hydroxy- Δ^2 -dihydrofuran-2,3-dicarboxylate (323).⁴³ The furan derivative (324) is formed on treatment of 323 with acid. Subsequent investigations have shown that a mixture

¹⁹⁴ R. K. Gupta and M. V. George, *Tetrahedron* **31**, 1263 (1975).

¹⁹⁵ R. K. Gupta and M. V. George, unpublished results.



of products consisting of the dihydrofuran (323), dimethyl (α -benzoyl)benzyloxymaleate (325), and 2,3-diphenyl-6-carbomethoxymethylene-5,6-dihydro-1,4-dioxin-5-one (326) are formed in this reaction (Scheme 48).¹⁹⁵

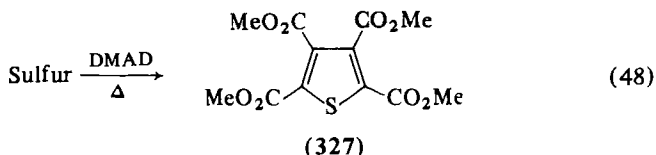


SCHEME 48

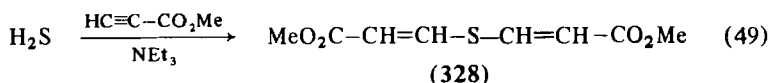
IV. Sulfur-Containing Nucleophiles

A. SULFUR, SULFIDES, AND SULFOXIDES

Michael,¹⁹⁶ as early as 1895, reported the reaction of elemental sulfur with DMAD to give tetramethyl 2,3,4,5-thiophenetetracarboxylate (327)

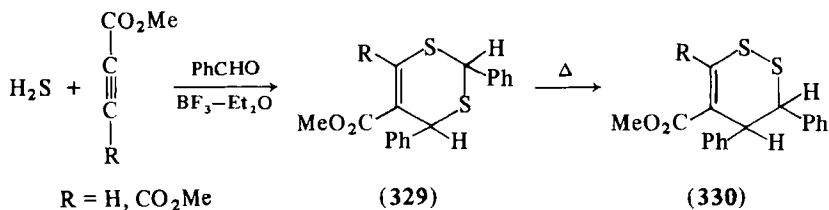


[Eq. (48)]. Several reactions of hydrogen sulfide with acetylenic esters have been studied. The reaction of hydrogen sulfide with methyl propiolate, for example, gives rise to a simple 1 : 2 adduct (328) [Eq. (49)].¹⁹⁷ In the presence of aromatic aldehydes, H₂S reacts with



acetylenic esters to give dithiin derivatives. Thus, the reaction of H₂S with DMAD in presence of benzaldehyde and a catalyst such as BF₃·Et₂O gives a 1,3-dithiin (329), which on heating rearranges to dimethyl 3,4-dihydro-3,4-diphenyl-1,2-dithiin-5,6-dicarboxylate (330) (Scheme 49).¹⁹⁸

The reaction of carbon disulfide with acetylenic esters gives a number of products, depending on the conditions.^{199,200} Thus, with DMAD



SCHEME 49

¹⁹⁶ A. Michael, *Ber.* **28**, 1633 (1895).

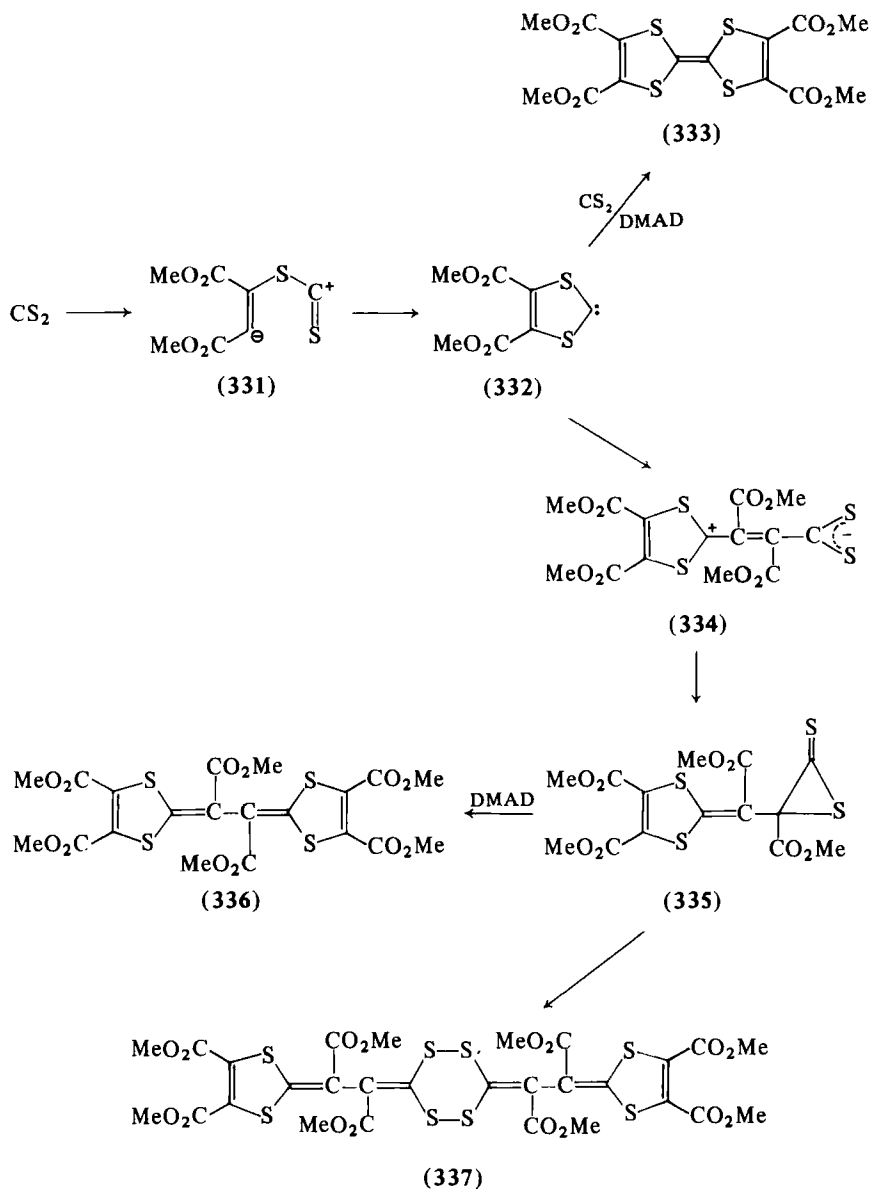
¹⁹⁷ W. Haefliger and T. Petrzilka, *Helv. Chim. Acta* **49**, 1937 (1966) [*CA* **66**, 10540 (1967)].

¹⁹⁸ (a) T. Krishnamurthy, Ph.D. Thesis, Howard Univ. (1971); *Diss. Abstr. B* **32**, 6300 (1972); (b) U. Eisner and T. Krishnamurthy, *Int. J. Sulfur Chem. (B)* **6**, 267 (1971) [*CA* **76**, 24978 (1972)].

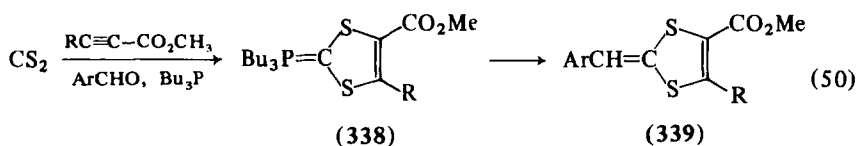
¹⁹⁹ D. L. Coffen, *Tetrahedron Lett.*, 2633 (1970).

²⁰⁰ H. D. Hartzler, *J. Amer. Chem. Soc.* **95**, 4379 (1973).

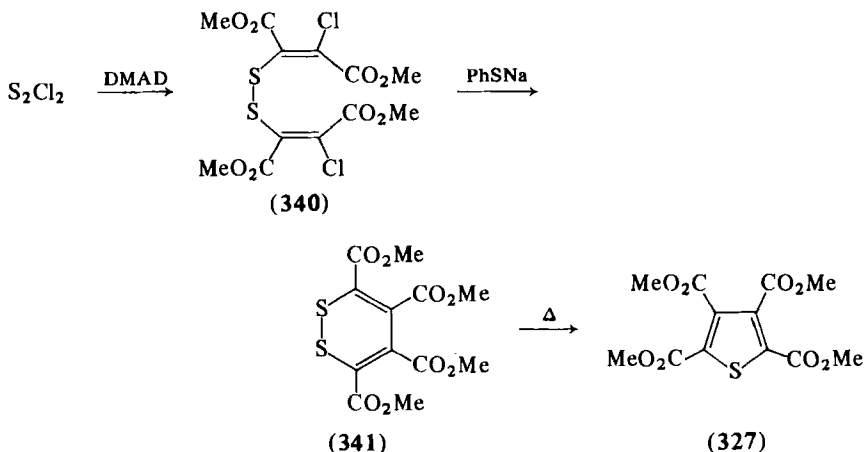
around 100° a mixture of the 2 : 3 adduct (336) and the 4 : 4 adduct (337) is formed. In acetic acid, however, the reaction gives the 2 : 2 adduct (333) (Scheme 50). The reaction of carbon disulfide with acetylenic esters in the presence of aromatic aldehydes and tributylphosphine



SCHEME 50



yields 2-benzylidene-1,3-dithiols (339) [Eq. (50)].²⁰¹ In the reaction of disulfur dichloride with DMAD, a 1 : 2 adduct (340), is formed, which on treatment with sodium thiophenolate gives tetramethyl 1,2-dithiin-3,4,5,6-tetracarboxylate (341). Heating 341 to about 135° results in tetramethyl thiophenetetracarboxylate (327) (Scheme 51).²⁰²



SCHEME 51

Winterfeldt²⁰³ has shown that the reaction of dimethyl sulfoxide with DMAD gives tetramethyl furantetracarboxylate (345), and it was suggested that this reaction may proceed through the intermediates 342, 343, and 344 (Scheme 52). The reaction of *t*-butylsulfenic acid with methyl propiolate, however, gives β,β' -bis(*trans*-carbomethoxy)divinyl sulfoxide (348) (Scheme 53).²⁰⁴ The penicillin S-oxide (349) is known to react with DMAD to give the adduct 352, and this reaction has been assumed to proceed through the sulfenic acid intermediate 350 (Scheme 54).²⁰⁵

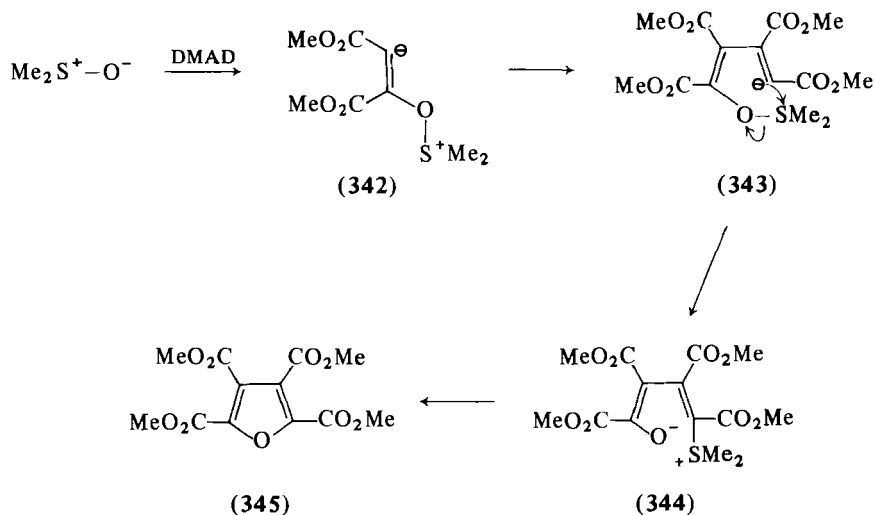
²⁰¹ H. D. Hartzler, *J. Amer. Chem. Soc.* **93**, 4961 (1971).

²⁰² W. Ried and W. Ochs, *Chem. Ber.* **105**, 1093 (1972).

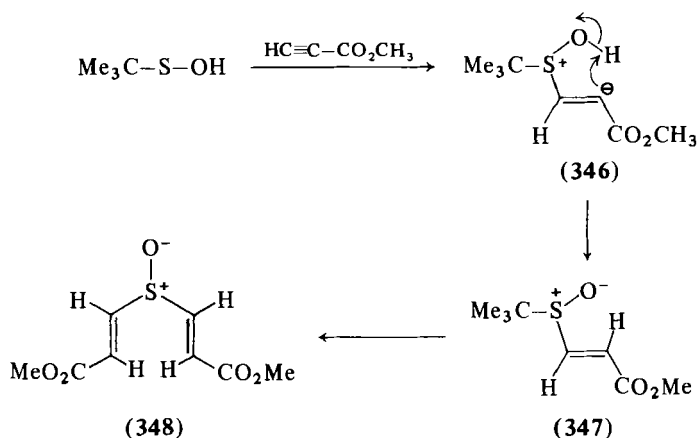
²⁰³ E. Winterfeldt, *Chem. Ber.* **98**, 1581 (1965).

²⁰⁴ J. R. Shelton and K. E. Davis, *J. Amer. Chem. Soc.* **89**, 718 (1967).

²⁰⁵ I. Ager, D. H. R. Barton, D. G. T. Greig, D. Lucente, P. G. Sammes, M. V. Taylor, G. H. Hewitt, B. E. Looker, A. Mowatt, C. A. Robson, and W. G. E. Underwood, *J. Chem. Soc., Perkin Trans. I*, 1187 (1973).



SCHEME 52



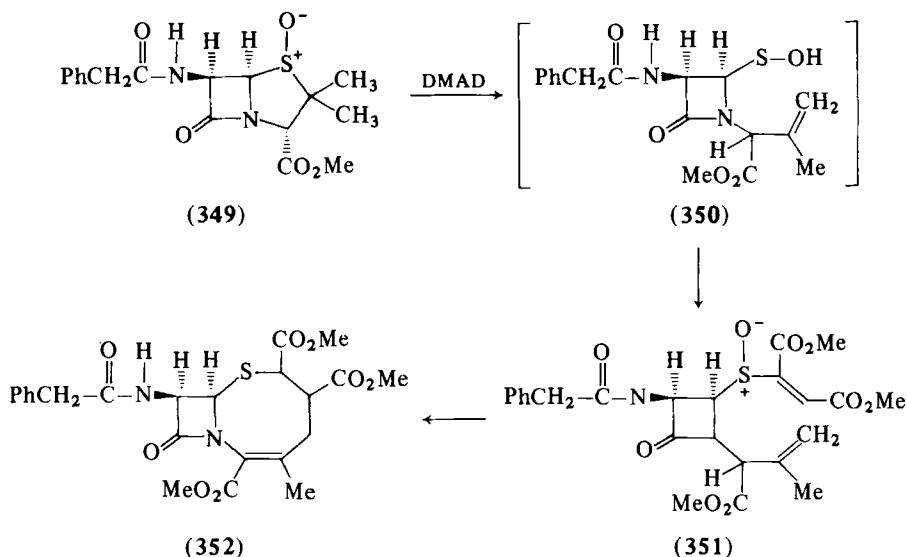
SCHEME 53

B. THIOLS

Ethyl mercaptan reacts with DMAD to give a 1 : 1 adduct through a trans mode of addition.²⁰⁶ Weibull²⁰⁷ has reported that a mixture of both fumarate and maleate is formed from cyclohexyl mercaptan with propiolic acid. A similar observation has been made in the reaction of cyclohexyl mercaptan with acetylenedicarboxylic acid.²⁰⁷

²⁰⁶ A. T. Blomquist and J. Wolinsky, *J. Org. Chem.* **23**, 551 (1958).

²⁰⁷ B. Weibull, *Arkiv Kemi* **3**, 225 (1951) [*CA* **46**, 3965 (1952)].



SCHEME 54

Mercaptoacetone reacts with methyl propiolate to give a 1 : 1 adduct, which then cyclizes to a substituted thiophene.²⁰⁸ Similar addition reactions of mercaptans with acetylenic acids have also been reported by Owen and Sultanbawa.²⁰⁹

Thiophenols undergo base-catalyzed, Michael addition to acetylenic acids and esters to give trans addition products.^{183,186,210-215} These vinyl thioethers have been used in the synthesis of thiochromones.^{186,211,213} Recently, Undheim and Lie²¹⁶ have shown that thiophenol adds to DMAD with concomitant cyclization to give benzo[*b*]thiophenes.

The reaction of several thiophenols containing suitably positioned functional groups with acetylenic esters give rise to several interesting products. The reaction of pentafluorothiophenol with diethyl acetylenedicarboxylate in the presence of butyl lithium yields 2,3-dicarbethoxy-4,5,6,7-tetrafluorobenzo[*b*]thiophene (353), formed by

²⁰⁸ F. Bohlmann and E. Bresinsky, *Chem. Ber.* **97**, 2109 (1964).

²⁰⁹ L. N. Owen and M. U. S. Sultanbawa, *J. Chem. Soc.*, 3109 (1949).

²¹⁰ F. Montanari, *Tetrahedron Lett.* **4**, 18 (1960).

²¹¹ S. Ruhemann, *Ber.* **46**, 3384 (1913).

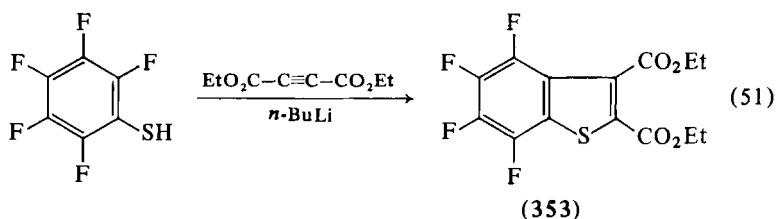
²¹² C. Finzi, G. Venturini, and L. Sartini, *Gazz. Chim. Ital.* **60**, 798 (1930) [*CA* **25**, 1526 (1931)].

²¹³ W. E. Truce, and R. B. Kruse, *J. Amer. Chem. Soc.* **81**, 5372 (1959).

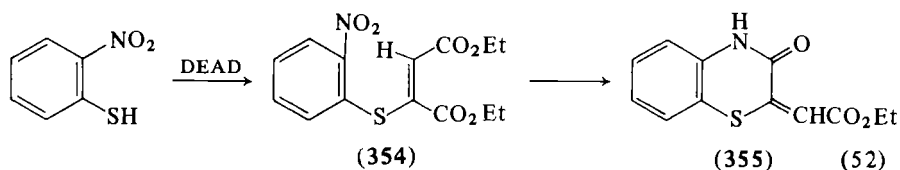
²¹⁴ W. E. Truce, D. L. Goldhamer, and R. B. Kruse, *J. Amer. Chem. Soc.* **81**, 4931 (1959).

²¹⁵ G. S. Krishnamurthy and S. I. Miller, *J. Amer. Chem. Soc.* **83**, 3961 (1961).

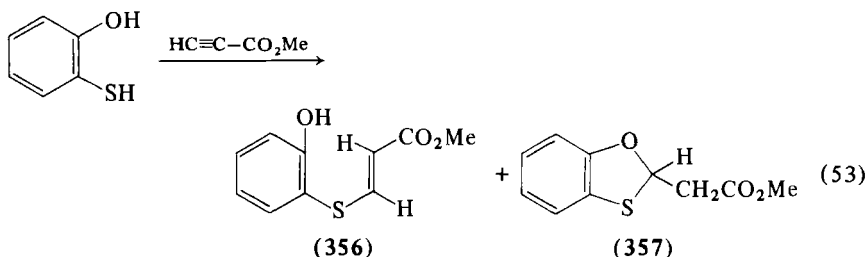
²¹⁶ R. Undheim and R. Lie, *Acta Chem. Scand.* **27**, 595 (1973).



displacement of a fluoride ion [Eq. (51)].²¹⁷ The reaction of *o*-nitrothiophenol with diethyl acetylenedicarboxylate gives a 1 : 1 adduct (354), which on catalytic reduction gives 2-carbethoxymethylene-3,4-dihydro-3-oxo-2*H*-benzo-1,4-thiazine (355) [Eq. (52)]. The same product



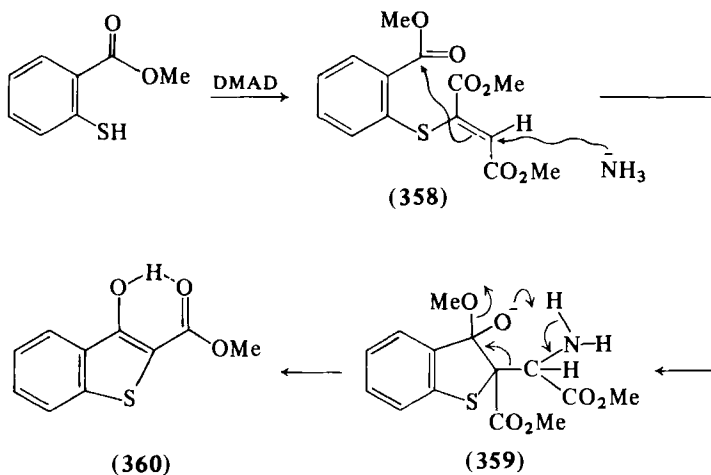
is obtained from the reaction of *o*-aminothiophenol with diethyl acetylenedicarboxylate.³⁸ The reaction of *o*-hydroxythiophenol with methyl propiolate, however, gives a mixture of the thioether (356) and 2-carbomethoxymethyl-1,3-benzoxathiole (357) [Eq. (53)].²⁰⁸



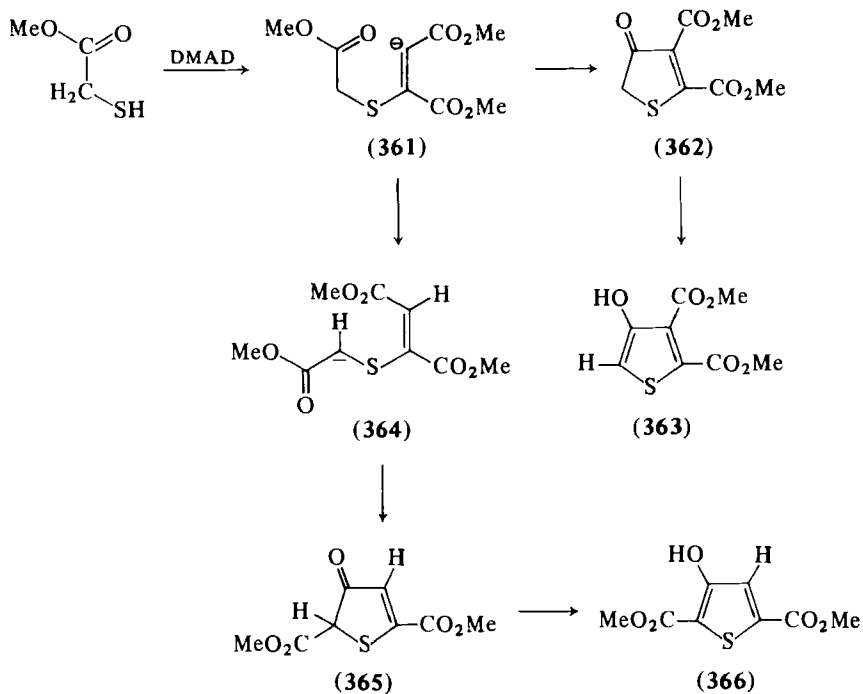
The reaction of methyl thiosalicylate with DMAD yields the Michael adduct (358), which undergoes cyclization on ammonolysis to give methyl 3-hydroxybenzo[*b*]thiophene-2-carboxylate (360) through the postulated intermediate 359 (Scheme 55).²¹⁸ On the other hand, the reaction of *o*-mercaptobenzamide with DMAD gives a 1 : 1 adduct (193) which is converted in the presence of base into the 1,3-benzothiazin-4-one derivative (194) [Eq. (31)].^{135,218} In the reaction of methyl

²¹⁷ G. M. Brooke and M. A. Quasem, *J. Chem. Soc. C*, 865 (1967).

²¹⁸ N. D. Heindel, V. B. Fish, M. F. Ryan, and A. R. Lepley, *J. Org. Chem.* **32**, 2678 (1967).



SCHEME 55

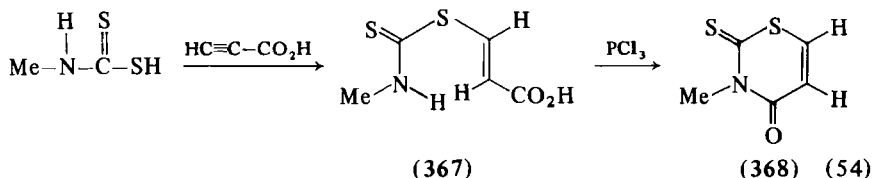


SCHEME 56

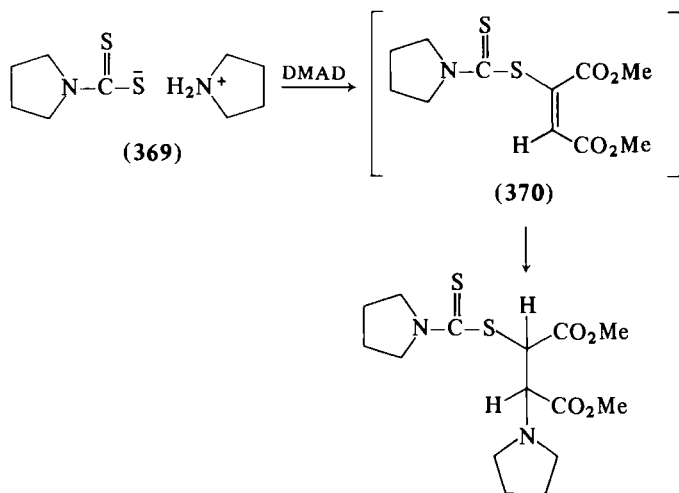
thioglycolate with DMAD, two isomeric thiophene derivatives, **363** and **366**, are formed, through the cyclization of carbanion intermediates like **361** and **364**, respectively (Scheme 56).²¹⁹⁻²²¹

C. THIOCARBAMATES AND THIUREAS

N-Methyldithiocarbamic acid reacts with propiolic acid to give β -(*N*-methylthiocarbamoylthio)acrylic acid (**367**), which when refluxed with phosphorus trichloride is cyclized to 3-methyl-3,4-dihydro-4-oxo-2-thiothiazine (**368**) [Eq. (54)].²²² It has recently been reported that



dithiocarbamates react with DMAD to give the corresponding α,β -disubstituted succinic esters. Thus, in the reaction of pyrrolidine dithiocarbamate (**369**) with DMAD, dimethyl α -pyrrolidino- β -pyrrolidine-dithiocarbamoylsuccinate (**371**) is formed (Scheme 57).²²³



SCHEME 57 (371)

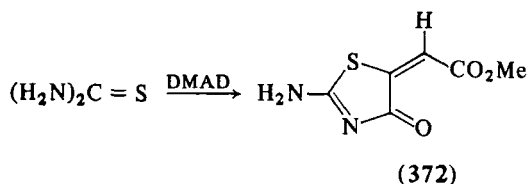
²¹⁹ (a) H. Fiesselmann and P. Schipprak, *Chem. Ber.* **87**, 835 (1954); (b) H. Fiesselmann, P. Schipprak, and L. Zeitler, *ibid.* **87**, 841 (1954).

²²⁰ H. Fiesselmann and P. Schipprak, *Chem. Ber.* **89**, 1897 (1956).

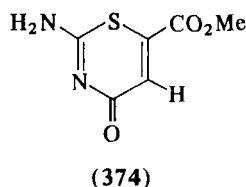
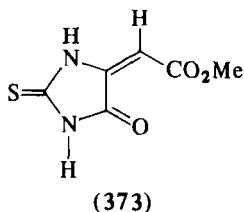
²²¹ H. Fiesselmann and W. Böhm, *Chem. Ber.* **89**, 1902 (1956).

²²² J. L. Garraway, *J. Chem. Soc.*, 4077 (1962).

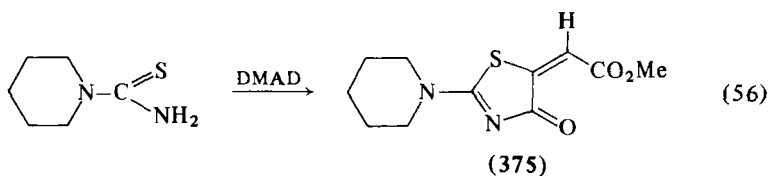
²²³ C. S. Angadiyavar, M. N. Gudi, and M. V. George, *Indian J. Chem.* **10**, 888 (1972).



(55)



The reaction of thiourea with acetylenic esters has been variously reported to give a thiazolin-4-one (372),^{43,224} an imidazolinethione (373),^{144,225} or a 1,3-thiazin-4-one (374)^{147,226-228} derivative. However, recent studies have shown that in fact it is the thiazolin-4-one (372) that is formed in this reaction [Eq. (55)].²²⁹ In the light of this observation, it may now be necessary to revise the structures of products obtained from the reaction of *N*-methylthiourea,¹⁴⁷ *N,N'*-dimethylthiourea,¹⁴⁷ and thiosemicarbazides¹⁴⁷ with acetylenic esters. The reaction of a thiourea derivative such as *N*-thiocarbamoylpiperidine with DMAD is reported to give 5-(carbomethoxymethylene)-2-piperidino- Δ^2 -1,3-thiazolin-4-one (375) [Eq. (56)].²³⁰



²²⁴ L. K. Mushkalo and G. Ya. Yangol, *Ukr. Khim. Zh.* **21**, 732 (1955) [*CA* **50**, 16751 (1956)].

²²⁵ H. Moriyama, *Yakugaku Zasshi* **83**, 169 (1963) [*CA* **59**, 3925 (1963)].

²²⁶ E. Winterfeldt and J. M. Nelke, *Chem. Ber.* **100**, 3671 (1967).

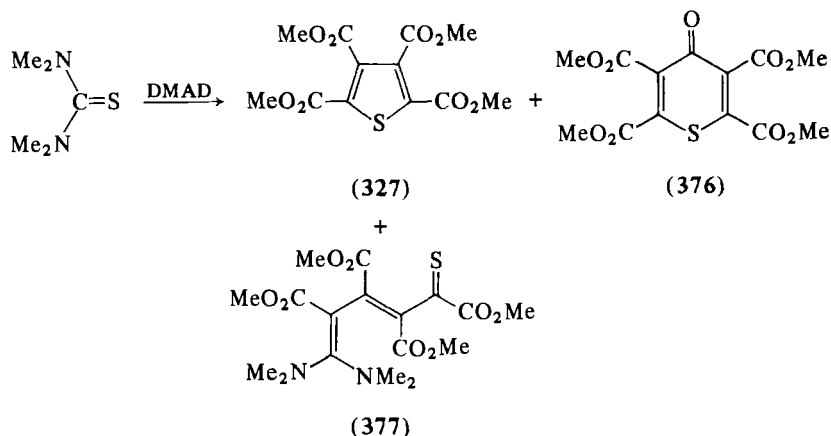
²²⁷ Y. Kishida and A. Terada, *Chem. Pharm. Bull.* **16**, 1351 (1968) [*CA* **69**, 95849 (1968)].

²²⁸ E. G. Kataev, L. K. Konovalova, and E. G. Yarkova, *Zh. Org. Khim.* **5**, 621 (1969) [*CA* **71**, 21668 (1969)].

²²⁹ F. W. Short, B. C. Littleton, and J. L. Johnson, *Chem. Ind. (London)*, 705 (1971).

²³⁰ A. F. Cameron, N. J. Hair, N. F. Elmore, and P. J. Taylor, *Chem. Commun.*, 890 (1970).

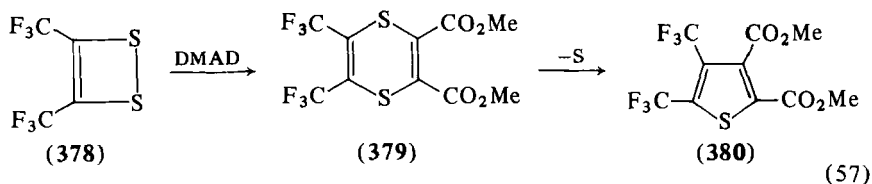
An interesting case of the reaction of tetramethylthiourea with DMAD has been reported by Winterfeldt.²³¹ The products formed in this reaction are tetracarbomethoxythiophene (327), 2,3,5,6-tetracarbomethoxy-4*H*-thiopyran-4-one (376), and an open-chain 1:2 adduct (377) (Scheme 58).



SCHEME 58

D. SULFUR HETEROCYCLES

Krespan and McKusick²³² have studied the addition reaction of dithietenes to various olefins and acetylenes. Thus, the reaction of 3,4-bis(trifluoromethyl)-1,2-dithiete (378) with DMAD gives a *p*-dithiin derivative (379), which loses sulfur on heating to give 2,5-dicarbomethoxy-4,5-bis(trifluoromethyl)thiophene (380) [Eq. (57)].

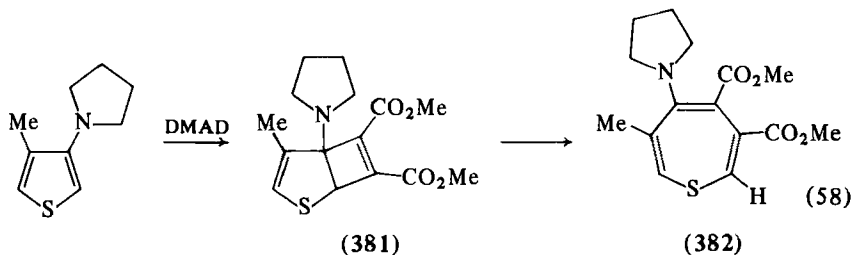


A thiopin derivative (**382**) has been reported to be formed in the reaction of 3-methyl-4-pyrrolidinylthiophene with DMAD. The initial adduct, 5-pyrrolidino-2-thiabicyclo[3.2.0]hepta-3,6-diene (**381**), formed around -30° , isomerizes to dimethyl 6-methyl-5-pyrrolidinylthieline-3,4-dicarboxylate (**382**) [Eq. (58)].²³³

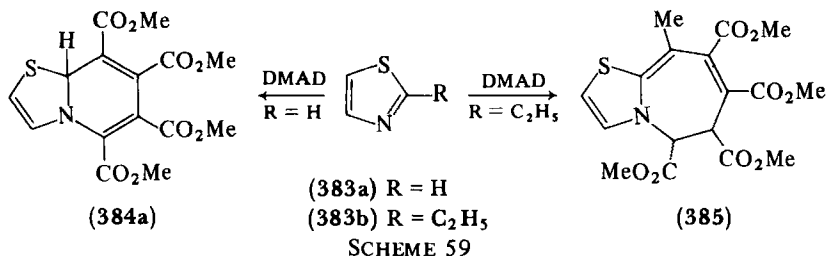
²³¹ E. Winterfeldt, *Chem. Ber.* **100**, 3679 (1967).

²³² C. G. Krespan and B. C. McKusick, *J. Amer. Chem. Soc.* **83**, 3438 (1961).

²³³ (a) D. N. Reinhoudt and C. G. Kouwenhoven, *Chem. Commun.* 1232 (1972); (b) 1233 (1972).



Addition reactions of several thiazole and benzothiazole derivatives to DMAD have been reported.^{234–236} Thiazole (383a), for example, gives a 1 : 2 adduct (384a) on treatment with DMAD,²³⁴ whereas in the reaction of 2-ethylthiazole (383b), a 5,6-dihydrothiazolo[3,2-*a*]azepine (385) is



formed (Scheme 59).²³⁵ Similarly, the reactions of benzothiazole (386a) and 2-methylbenzothiazole (386b) with DMAD give the corresponding adducts, 387 and 338, respectively (Scheme 60).²³⁶

Easton *et al.*²³⁷ have studied the reaction of 1,3-dithiolane-2-thione (389a) with DMAD and have observed the formation of dimethyl 1,3-dithiole-2-thione-4,5-dicarboxylate (390a) with the elimination of ethylene moiety. Similarly, the reaction of 1,3-oxathiolane-2-thione (389b) with DMAD gives 2-oxo-1,3-dithiole-4,5-dicarboxylate (390b).²³⁸ On the other hand, the imidazolidinethione (391) reacts with DMAD to give 2,3-dihydro-6-carbomethoxyimidazo[2,1-*b*]thiazin-4-one (392) (Scheme 61).¹⁰⁶ Simple 1 : 1 adducts (394), however, have been obtained in the reaction of benzothiazole-2-thione (393a) and benzimidazole-2-thione (393b) with ethyl propiolate [Eq. (59)].^{239,240}

²³⁴ D. H. Reid, F. S. Skelton, and W. Bonthron, *Tetrahedron Lett.*, 1797 (1964).

²³⁵ C. Divorve, P. Joly, and J. Roggero, *C. R. Acad. Sci., Ser. C*, 271, 763 (1970) [CA 74, 13047 (1971)].

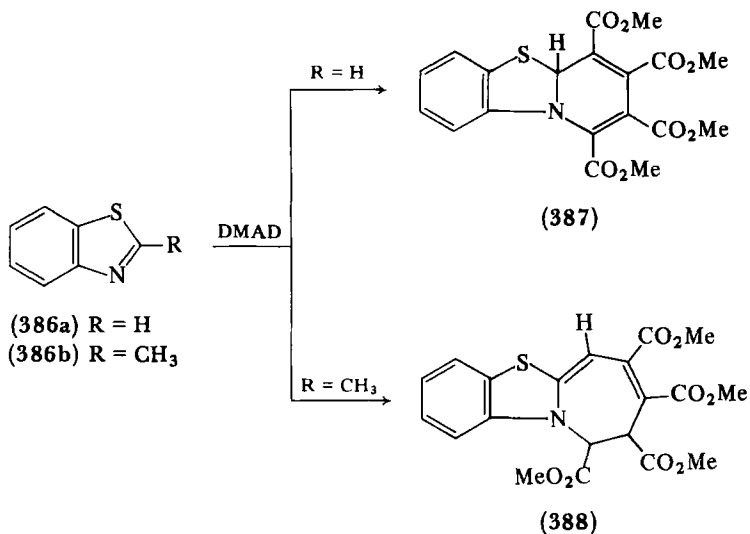
²³⁶ R. M. Acheson, M. W. Foxton, and G. R. Miller, *J. Chem. Soc.*, 3200 (1965).

²³⁷ D. B. J. Easton, D. Leaver, and T. J. Rawlings, *J. Chem. Soc., Perkin Trans. I*, 41 (1972).

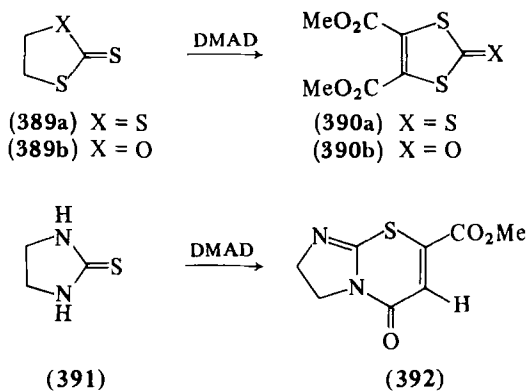
²³⁸ B. R. O'Connor and F. N. Jones, *J. Org. Chem.* 35, 2002 (1970).

²³⁹ E. I. Grinblat and I. Ya. Postovskii, *Dokl. Akad. Nauk SSSR* 133, 847 (1960) [CA 54, 24756 (1960)].

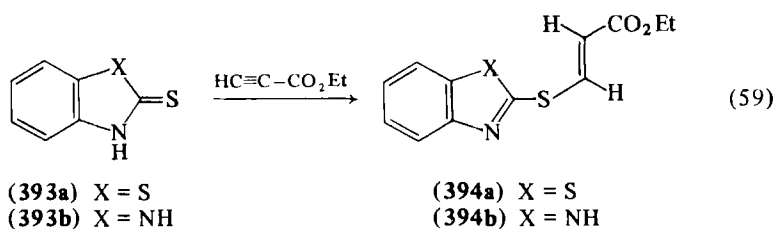
²⁴⁰ E. I. Grinblat and I. Ya. Postovskii, *Zh. Obshch. Khim.* 31, 394 (1961) [CA 55, 22298 (1961)].



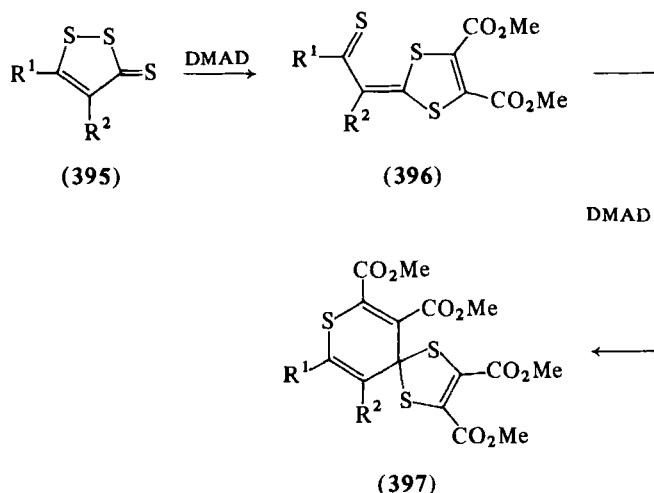
SCHEME 60



SCHEME 61

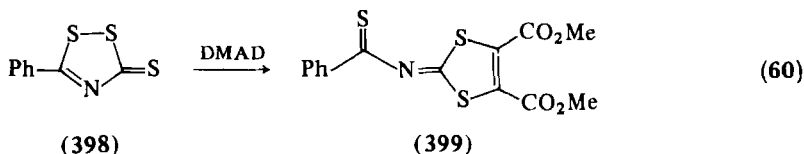


Several workers have studied the reactions of 1,2-dithiole-3-thiones and related systems with acetylenic esters.^{237,241-244} The thiones (395), for example, react with DMAD to give 2-thioacylmethylene-1,3-dithioles (396), which may arise through a concerted 1,3-dipolar addition to the S=C=S moiety. These adducts undergo further reaction with DMAD, yielding thiopyran-4-spiro-2'-(1,3-dithioles) (397) (Scheme 62).²³⁷ Similarly, the reaction of 5-phenyl-1,2,4-dithiazole-3-thione (398) with



SCHEME 62

DMAD gives the adduct (399) [Eq. (60)].²⁴⁵ The reaction of 5-amino-1,2,4-dithiazole-3-thione (400) with DMAD, however, gives rise to the initial adduct (401), which further reacts with DMAD to give 402



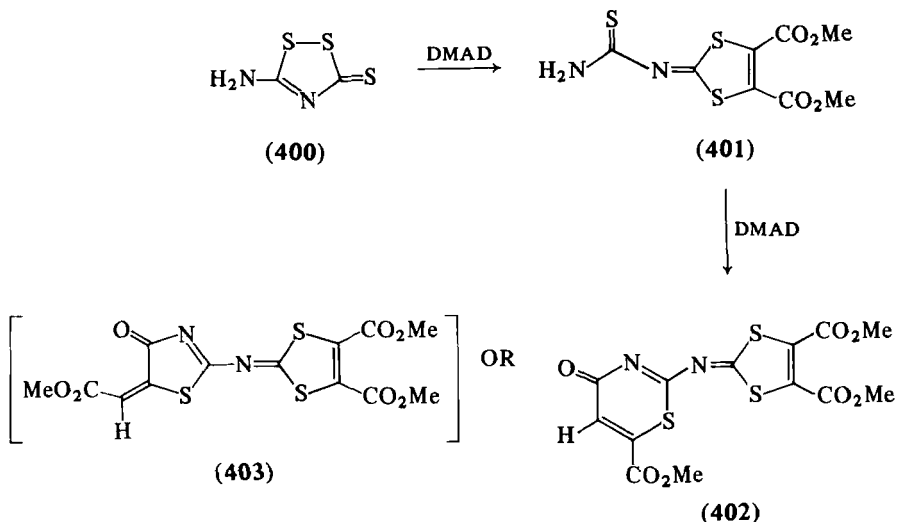
²⁴¹ D. B. J. Easton and D. Leaver, *Chem. Commun.*, 585 (1965).

²⁴² H. Behringer and R. Wiedenmann, *Tetrahedron Lett.*, 3705 (1965).

²⁴³ H. Behringer, D. Bender, J. Falkenburg, and R. Wiedenmann, *Chem. Ber.* 101, 1428 (1968).

²⁴⁴ (a) H. Davy, M. Demynck, D. Paquer, A. Ronessac, and J. Vialle, *Bull. Soc. Chim. Fr.*, 1150 (1966) [*CA* 65, 697 (1966)]; (b) 2057 (1968) [*CA* 69, 86866 (1968)].

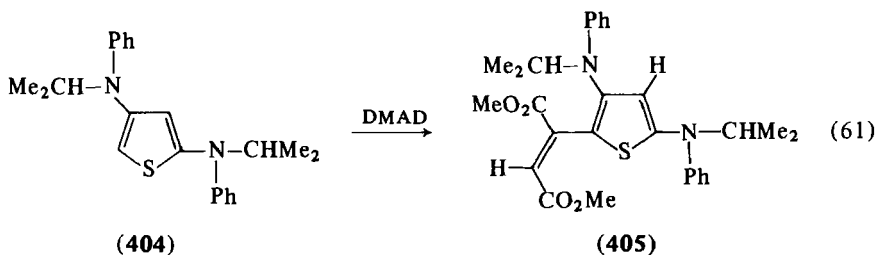
²⁴⁵ H. Behringer and D. Deichmann, *Tetrahedron Lett.*, 1013 (1967).



SCHEME 63

(Scheme 63).²⁴³ The alternative structure (403) for the final product should also be considered in the light of the structural revision of the adduct obtained from thiourea and DMAD.²²⁹

A Michael type of addition is observed in the reaction of *N,N'*-diisopropyl-*N,N'*-diphenyl-2,4-thiophenediamine (404) with DMAD to give the 1 : 1 adduct (405) [Eq. (61)].²⁴⁶



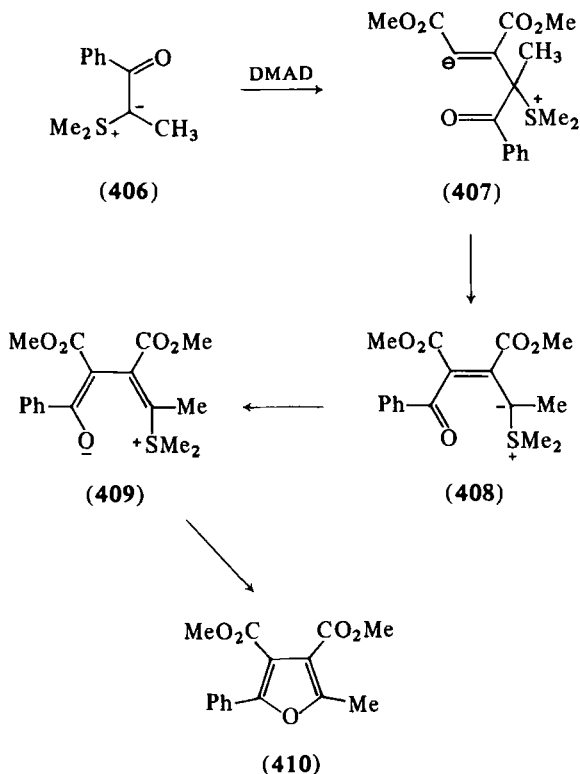
E. SULFONIUM YLIDES

Winterfeldt²⁰³ has postulated the intermediacy of sulfonium ylides in the reaction of dimethyl sulfoxide with DMAD, yielding furan derivatives (Scheme 52). Similarly, it has been shown that sulfonium diacetylmethylides, like the dibenzoylmethylide, react with acetylenic esters to give furan derivatives.²⁴⁷ In the reaction of sulfonium α -methylphenacylide with

²⁴⁶ J. P. Chupp, *J. Heterocycl. Chem.* **9**, 1033 (1972).

²⁴⁷ M. Takaku, Y. Hayasi, and H. Nozaki, *Tetrahedron Lett.*, 2053 (1969).

DMAD, dimethyl 2-methyl-5-phenylfuran-3,4-dicarboxylate (**410**) is formed. It has been suggested that the reaction proceeds through the betaine (**407**), which is transformed into the ylide (**408**) and so into the furan (**410**) (Scheme 64).²⁴⁸ By carrying out the reaction in benzene it was possible to isolate the ylide (**408**) and thereby substantiate the suggested mechanism.

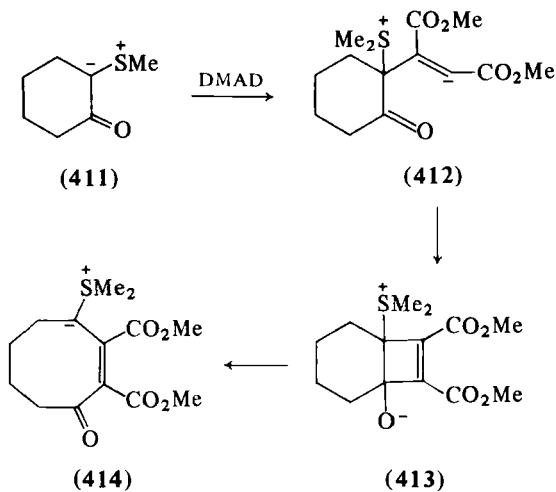


SCHEME 64

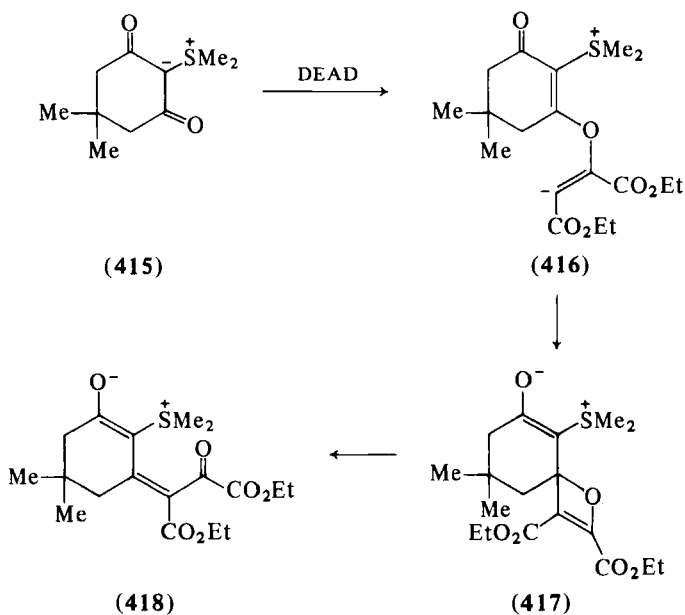
The reaction of a cyclic sulfonium ylide such as dimethylsulfonium-2-oxocyclohexylide (**411**) with DMAD gives rise to a ring-expanded product, namely, dimethylsulfonium-2,3-dicarbomethoxy-4-oxo-2-cyclooctenylide (**414**), probably through the intermediates **412** and **413** (Scheme 65).²⁴⁹ By carrying out the reaction in benzene, it was possible to isolate a compound assumed to be **413**, which was subsequently transformed in polar solvents to **414**. The reaction of an analogous ylide

²⁴⁸ M. Higo and T. Mukaiyama, *Tetrahedron Lett.*, 2565 (1970).

²⁴⁹ M. Higo, T. Sakashita, M. Toyoda, and T. Mukaiyama, *Bull. Chem. Soc. Jap.* **45**, 250 (1972).

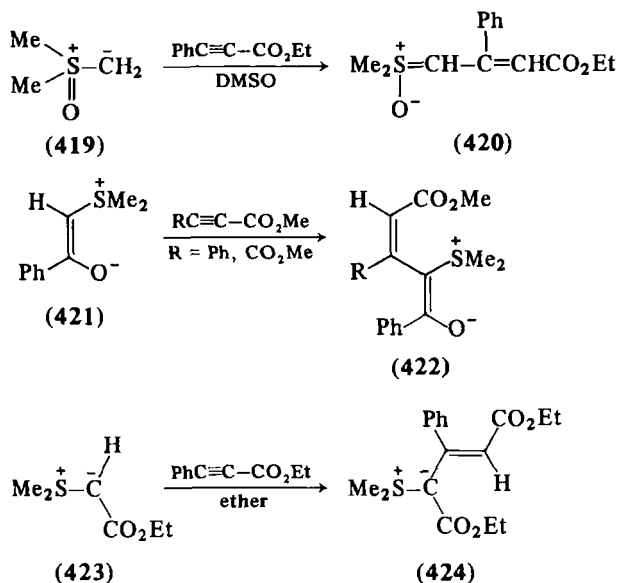


SCHEME 65



SCHEME 66

(415) with diethyl acetylenedicarboxylate, however, gives rise to an exomethylene ylide (418) (Scheme 66).²⁴⁷ In the reaction of dimethylsulfoxoniummethylide (419),^{250,251} dimethylsulfoniumphenacylide (421),²⁵² and ethyl (dimethylsulfuranylidene)acetate (423)²⁵³ with acetylenic esters, however, stable, open-chain ylides 420, 422, and 424 are formed (Scheme 67).



SCHEME 67

V. Phosphorus-Containing Nucleophiles

A. PHOSPHINES

Reactions of several phosphorus-containing nucleophiles with acetylenic esters are reported in the literature. Tertiary phosphines react with acetylenic esters, yielding a variety of products, depending on the reaction conditions. The reaction of triphenylphosphine with DMAD, for example, in ether around -50° gives an unstable 1 : 2 adduct, formulated as cyclopropenylmethylidenephosphorane (425), which on

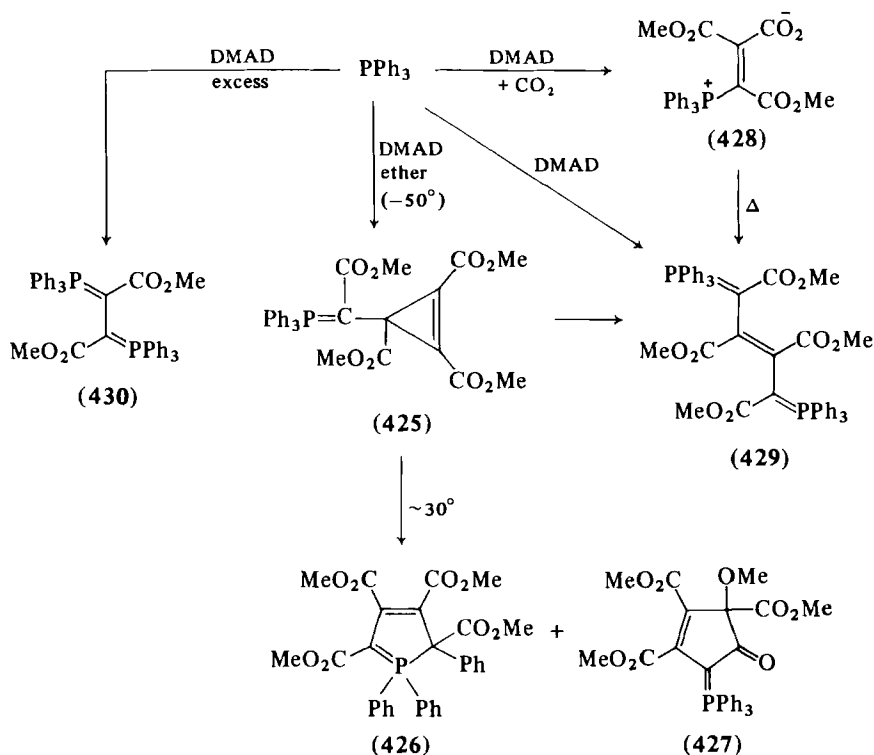
²⁵⁰ C. Kaiser, B. M. Trost, J. Beeson, and J. Weinstock, *J. Org. Chem.* **30**, 3972 (1965).

²⁵¹ J. Ide and Y. Kishida, *Tetrahedron Lett.*, 1787 (1966).

²⁵² B. M. Trost, *J. Amer. Chem. Soc.* **89**, 138 (1967).

²⁵³ G. B. Payne, *J. Org. Chem.* **33**, 3517 (1968).

warming to room temperature is transformed into a mixture of two stable adducts, namely, tetramethyl 1,1,2-triphenyl-2*H*-phosphole-2,3,4,5-tetracarboxylate (426)²⁵⁴⁻²⁵⁷ and trimethyl 3-methoxy-4-oxo-5-(triphenylphosphoranylidene)-1-cyclopentene-1,2,3-tricarboxylate (427).^{258,259} The unstable adduct (425) also reacts with triphenylphosphine in a manner characteristic of activated cyclopropenes to give tetramethyl 1,4-bis(triphenylphosphoranylidene)but-2-ene-1,2,3,4-tetracarboxylate (429).²⁵⁹ The 1,4-diphosphorane (429) has also been obtained by the decarboxylative dimerization of the 1 : 1 : 1 betaine (428),



SCHEME 68

²⁵⁴ A. W. Johnson and J. C. Tebby, *J. Chem. Soc.*, 2126 (1961).

²⁵⁵ J. B. Hendrickson, R. E. Spenger, and J. J. Sims, *Tetrahedron* **19**, 707 (1963).

²⁵⁶ N. E. Waite, J. C. Tebby, R. S. Ward, and D. H. Williams, *J. Chem. Soc., C*, 1100 (1969).

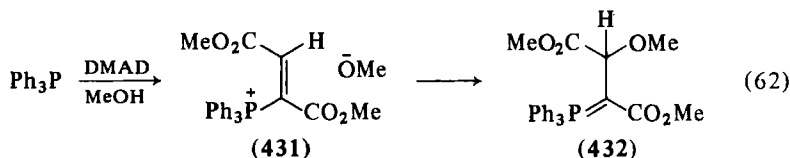
²⁵⁷ J. C. Tebby, *Chem. Soc. Int. Symp. Ylides*, July 1970.

²⁵⁸ N. E. Waite, J. C. Tebby, R. S. Ward, M. A. Shaw, and D. H. Williams, *J. Chem. Soc., C*, 1620 (1971).

²⁵⁹ N. E. Waite, D. W. Allen, and J. C. Tebby, *Phosphorus* **1**, 139 (1971) [*CA* **76**, 46258 (1972)].

formed from the reaction of triphenylphosphine with DMAD in presence of carbon dioxide.²⁶⁰ On the other hand, when an excess of triphenylphosphine is treated with DMAD, a stable 1,2-diphosphorane (430) is obtained (Scheme 68).²⁶¹

Wilson and Tebby²⁶² have studied the reaction of triphenylphosphine with different acetylenic esters in alcohol medium and have shown that β -alkoxyvinylphosphonium ylides and vinyl ethers are formed through the alcoholysis of vinyl phosphonium intermediates. Thus, triphenylphosphine reacts with DMAD in methanol to give the phosphorane (432) [Eq. (62)]. The reaction with propiolic esters, on the



other hand, gives vinyl ethers. The reaction of triphenylphosphine with DMAD in D_2O is reported to give deuterated olefinic derivatives, again formed through a phosphonium hydroxide intermediate.²⁶³

An interesting reaction involving the formation of a pyrazole derivative (436) is observed when triphenylphosphine reacts with DMAD in presence of diethyl azodicarboxylate.²⁶⁴ This reaction is thought to proceed through the intermediates 433–435 (Scheme 69). Similarly, Winterfeldt and Dillinger⁷² have shown that the reaction of triphenylphosphine with DMAD in presence of benzaldehyde gives the lactone 439, presumably through the intermediates 437 and 438 (Scheme 70). Hughes and Davies²⁶⁵ have observed an unusual reaction of diphenylvinylphosphine with DMAD in moist ether, resulting in a mixture of phosphine oxides 442 and 444. The phosphine oxide 442 could arise through a hydrolytic cleavage of the dihydrophosphole 441, whereas 444 may arise through the phosphorane intermediate 443, formed by the Diels–Alder addition of the phosphole 440 with DMAD (Scheme 71).

²⁶⁰ M. A. Shaw, J. C. Tebby, J. Ronayne, and D. H. Williams, *J. Chem. Soc., C*, 944 (1967).

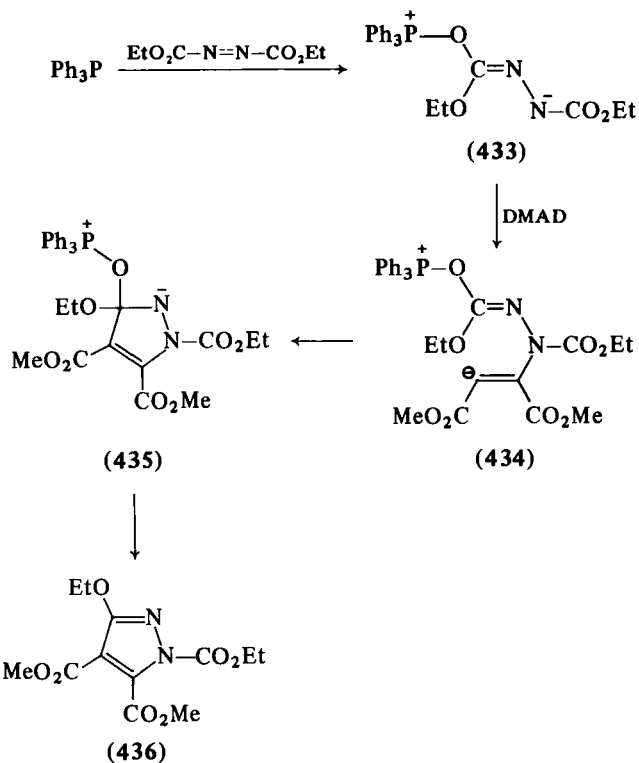
²⁶¹ M. A. Shaw, J. C. Tebby, R. S. Ward, and D. H. Williams, *J. Chem. Soc., C*, 2442 (1967).

²⁶² I. F. Wilson and J. C. Tebby, *J. Chem. Soc., Perkin Trans. I*, 2830 (1972).

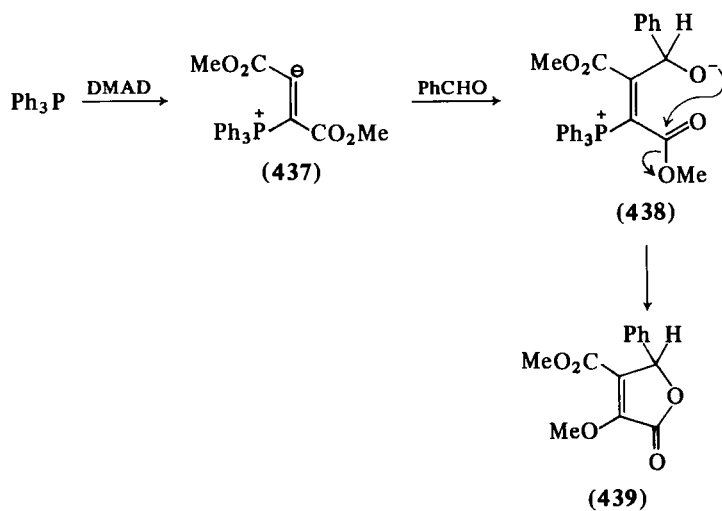
²⁶³ E. M. Richards, J. C. Tebby, R. S. Ward, and D. H. Williams, *J. Chem. Soc., C*, 1542 (1969).

²⁶⁴ R. C. Cookson and J. M. Locke, *J. Chem. Soc.*, 6062 (1963).

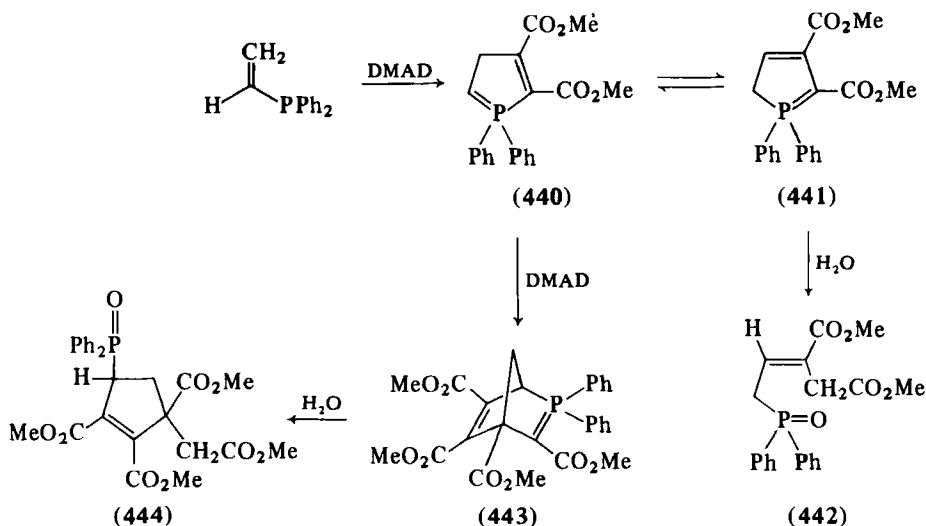
²⁶⁵ A. N. Hughes and M. Davies, *Chem. Ind. (London)*, 138 (1969).



SCHEME 69

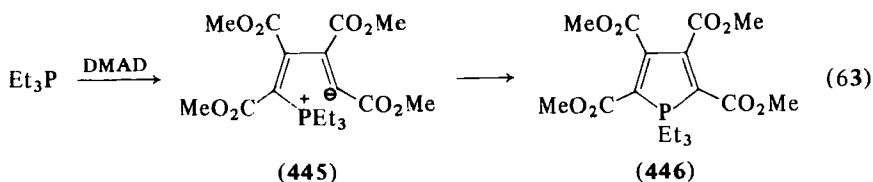


SCHEME 70

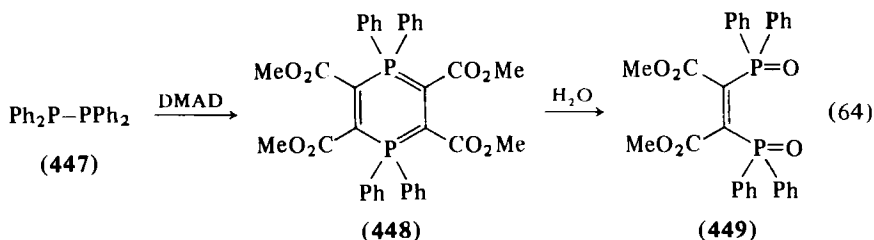


SCHEME 71

The reaction of triethylphosphine with DMAD gives the phosphole (446),²⁵⁵ which was earlier formulated as (445) [Eq. (63)].²⁶⁶

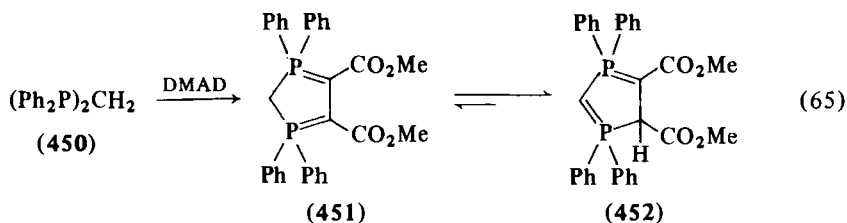


The reaction of tetraphenylbisphosphine (447) with excess of DMAD gives the phosphine oxide 449, presumably formed through the intermediate phosphorane (448) [Eq. (64)].²⁶⁷ On the other hand, the reac-

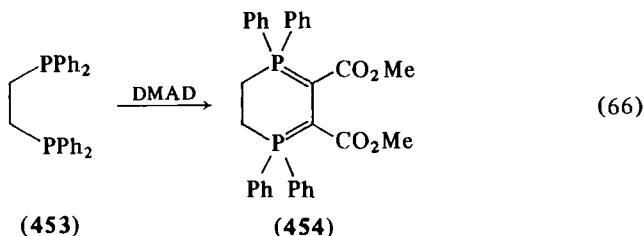


²⁶⁶ L. Horner and H. Hoffmann, *Angew. Chem.* **68**, 473 (1956).

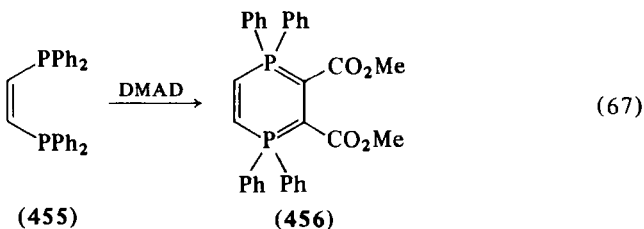
²⁶⁷ (a) S. W. S. Jafry, M.Sc. Thesis, Lakehead Univ., Canada, 1971; (b) M. Davies and A. N. Hughes, *J. Heterocycl. Chem.* **9**, 1 (1972).



tion of bis(diphenylphosphino)methane (450) with DMAD gives the 5H-1,3-diphosph(V)ole (452), probably formed through the bisphosphorane (451) [Eq. (65)].²⁶⁸ Similarly, the reaction of bis(diphenylphosphino)ethane (453) with DMAD gives the dihydro-1,4-diphosphorin (454) [Eq. (66)].²⁶⁹ In the reaction of *cis*-1,2-bis(diphenyl-



phosphino)ethylene (455) with DMAD, a 1,4-diphosph(V)orin (456) is formed [Eq. (67)],²⁶⁸ whereas *trans*-1,2-(diphenylphosphino)ethylene (457) gives the phosphine oxide 442, probably through the intermediates 458 and 459 (Scheme 72).²⁶⁷



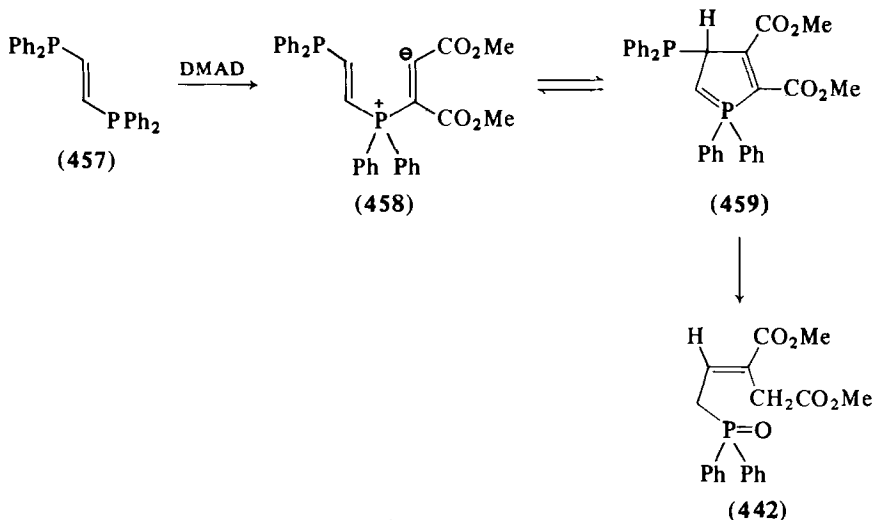
Diphenylphosphine oxide reacts with diethyl acetylenedicarboxylate to give a 2 : 1 adduct (460), and it has been suggested that in this reaction the phosphine oxide reacts in the tervalent form [Eq. (68)].²⁷⁰ On the

²⁶⁸ M. A. Shaw, J. C. Tebby, R. S. Ward, and D. H. Williams, *J. Chem. Soc., C*, 504 (1970).

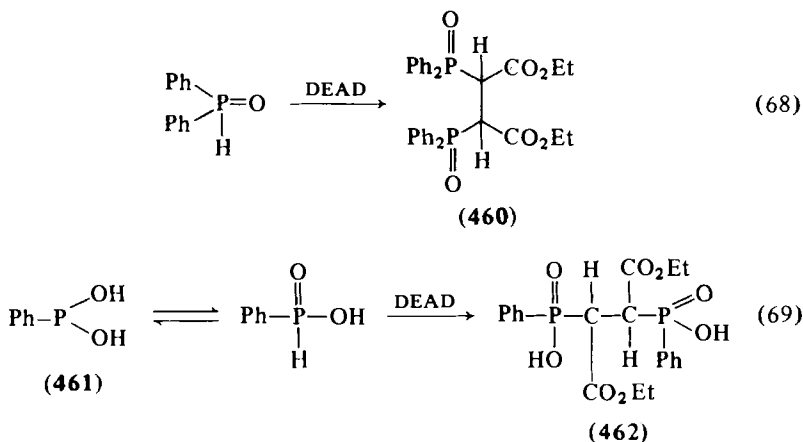
²⁶⁹ A. N. Hughes and S. W. S. Jafry, *J. Heterocycl. Chem.* **6**, 991 (1969).

²⁷⁰ I. G. M. Campbell and I. D. R. Stevens, *Chem. Commun.*, 505 (1966).

other hand, phenylphosphonous acid (461) reacts with diethyl acetylenedicarboxylate to give diphosphinic acid (462) [Eq. (69)].²⁷¹ The adduct is probably obtained as the racemic form, though its configuration has not been confirmed.



SCHEME 72

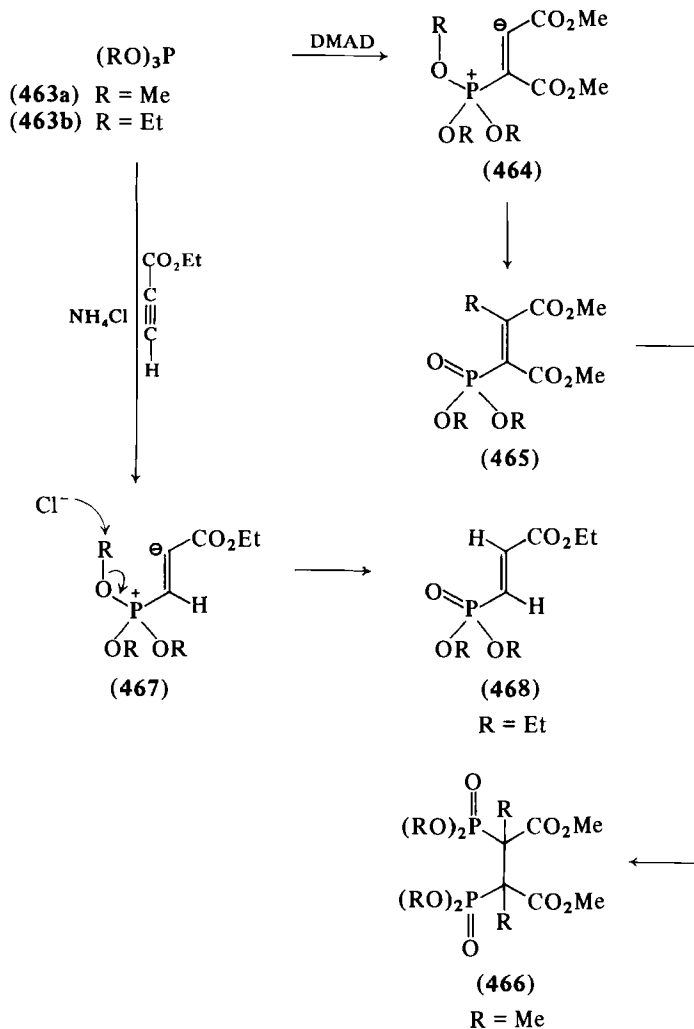


B. PHOSPHITES AND PHOSPHONATES

The reaction of trialkyl phosphites with acetylenic esters give different products, depending on the reaction conditions. Thus, the reaction of

²⁷¹ I. G. M. Campbell and S. M. Raza, *J. Chem. Soc., C*, 1836 (1971).

trimethyl phosphite (**463a**) with DMAD results in the formation of a succinate derivative (**466**).²⁷² On the other hand, the reaction of triethyl phosphite (**463b**) with ethyl propiolate in presence of ammonium chloride gives the adduct **468** (Scheme 73).²⁷³

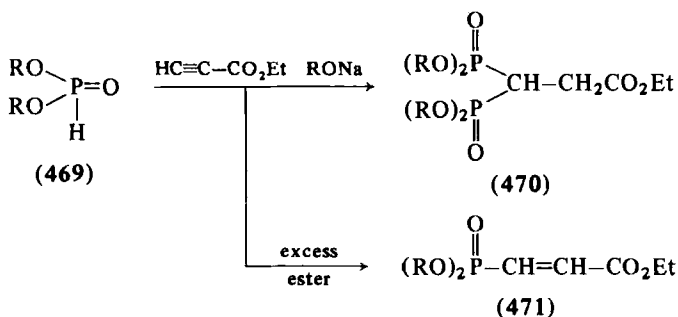


SCHEME 73

²⁷² C. E. Griffin and T. D. Mitchell, *J. Org. Chem.* **30**, 2829 (1965).

²⁷³ K. C. Pande, *Chem. Ind. (London)*, 1048 (1968).

Pudovik and Kuzovleva²⁷⁴ have studied the reaction of dialkyl phosphonates with ethyl propiolate and have shown that, in the presence of sodium alkoxide, a bis adduct (470) is formed, whereas with excess of the ester, under similar conditions, a mono adduct (471) is formed (Scheme 74).



SCHEME 74

C. ALKYLIDENE PHOSPHORANES AND PHOSPHINIMINES

The reactions of various triphenylalkylidenephosphoranes with acetylenic esters have been studied.²⁷⁵⁻²⁷⁷ In general, it has been found that the products formed in these reactions are to a large extent influenced by the nature of the solvent employed. Thus, the reaction of triphenylphosphorylideneacetophenone (472) with DMAD in an aprotic solvent such as dry ether gives the phosphorane 474, through the cyclic phosphorane 473. In contrast, the reaction of 472 in a protic solvent like methanol gives the Michael adduct (475) (Scheme 75).²⁷⁷

Triphenylphosphinimines (476) react with DMAD to give phosphoranes of the type 478 [Eq. (70)].²⁷⁸⁻²⁸¹ It has been reported that a phosphazine, such as 479, reacts with DMAD to give the adduct 480, which is transformed to the pyrazole 481 on heating [Eq. (71)].²⁷⁸

²⁷⁴ A. N. Pudovik and R. G. Kuzovleva, *Zh. Obshch. Khim.* 35, 354 (1965) [CA 62, 13175 (1965)].

²⁷⁵ S. Trippett, *J. Chem. Soc.*, 4733 (1962).

²⁷⁶ H. J. Bestmann and O. Rothe, *Angew. Chem.* 76, 569 (1964); *Angew. Chem., Int. Ed. Engl.* 3, 512 (1964).

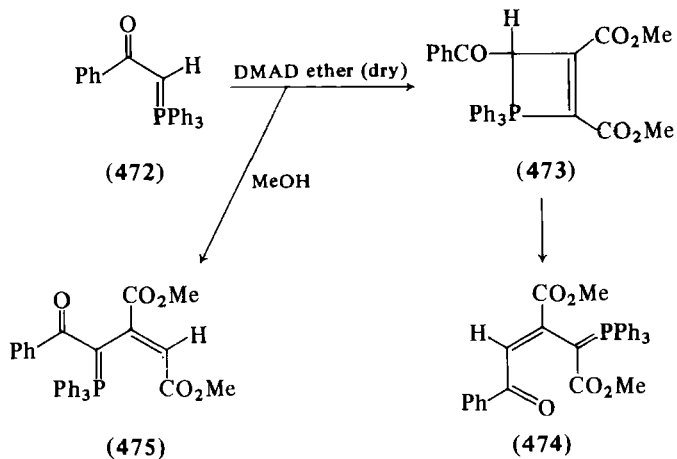
²⁷⁷ J. B. Hendrickson, C. Hall, R. Rees, and J. F. Templeton, *J. Org. Chem.* 30, 3312 (1965).

²⁷⁸ G. W. Brown, R. C. Cookson, and I. D. R. Stevens, *Tetrahedron Lett.*, 1263 (1964).

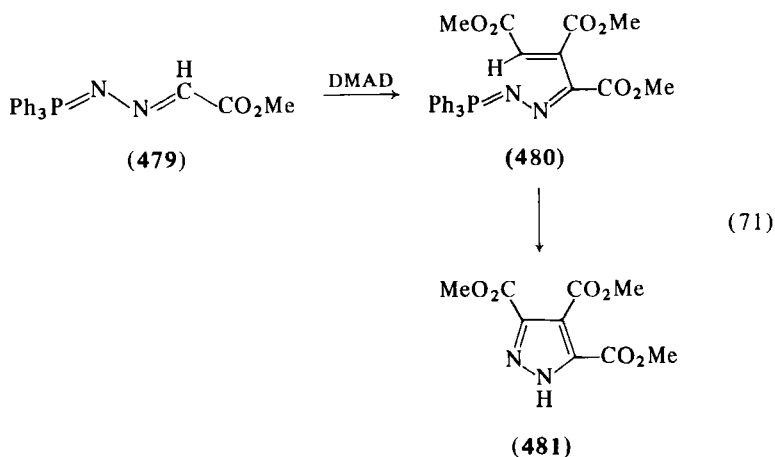
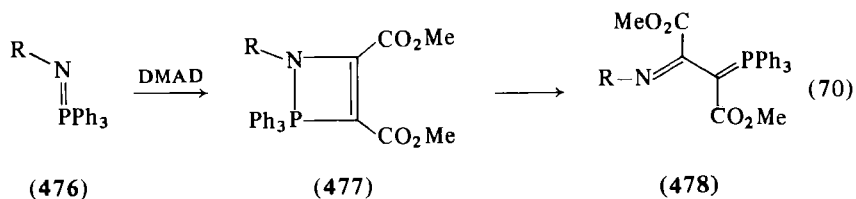
²⁷⁹ G. W. Brown, R. C. Cookson, I. D. R. Stevens, T. C. W. Mak, and J. Trotter, *Proc. Chem. Soc.*, 87 (1964).

²⁸⁰ T. C. W. Mak, and J. Trotter, *Acta Cryst.* 18, 81 (1965).

²⁸¹ G. W. Brown, *J. Chem. Soc., C*, 2018 (1967).

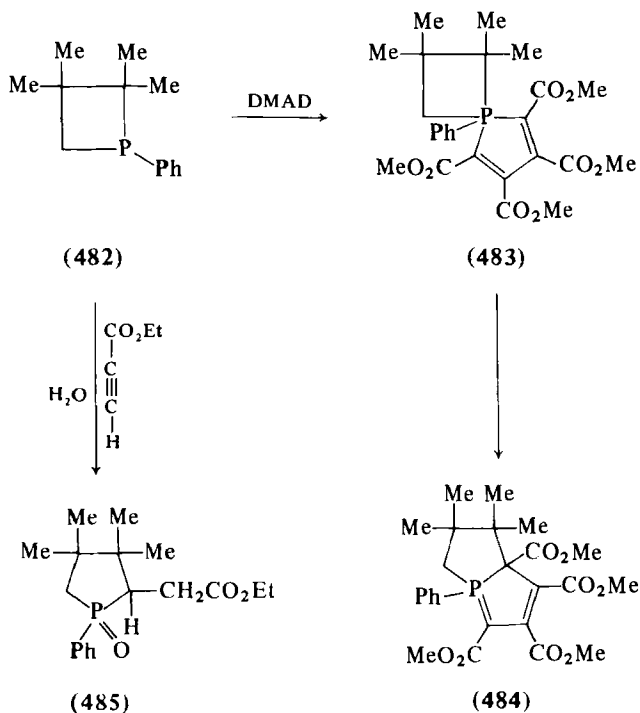


SCHEME 75



D. PHOSPHORUS HETEROCYCLES

Trippett *et al.*²⁸²⁻²⁸⁴ have observed both ring-opening and ring-expansion reactions when phosphetans are treated with acetylenic esters. Thus, the reaction of 2,2,3,3-tetramethyl-1-phenylphosphetan (482) with DMAD results in the formation of the phosphorane 484, probably through the bipyramidal spiroporphorane (483). The reaction of 482 with ethyl propiolate in wet ether, on the other hand, yields the cyclic phosphine oxide 485 (Scheme 76).²⁸² Similarly, the reactions of 2,2,3-trimethyl-1-phenylphosphetan²⁸² and 2,2,3,4,4-pentamethyl-1-phenylphosphetan²⁸³ with ethyl propiolate give the phosphine oxides corresponding to 485.



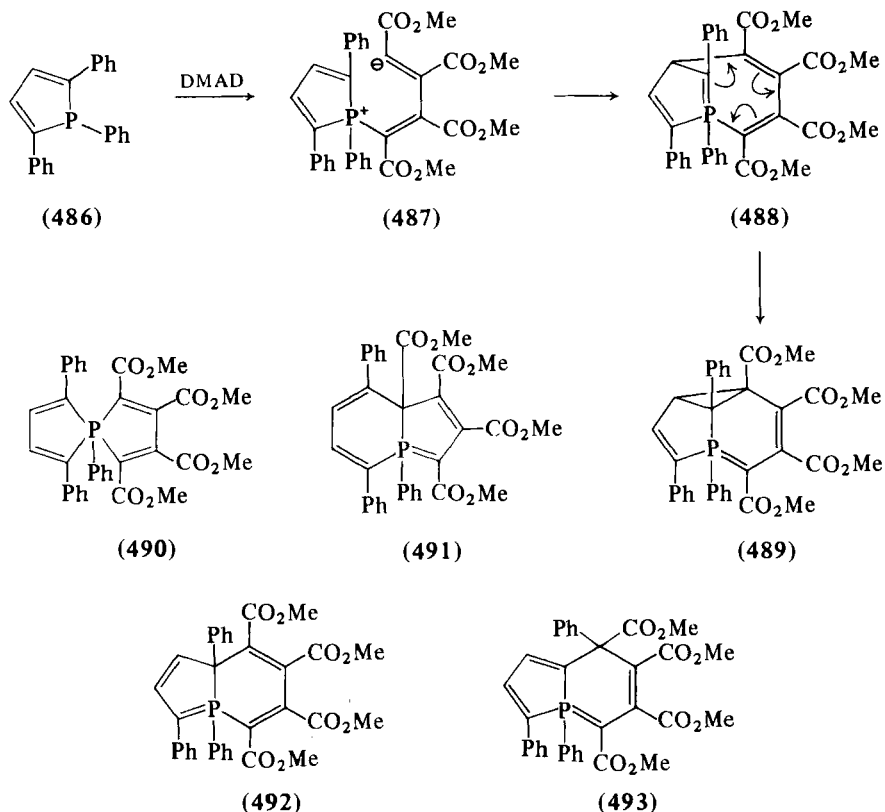
SCHEME 76

²⁸² J. R. Corfield, M. J. P. Harger, J. R. Shutt, and S. Trippett, *J. Chem. Soc., C*, 1855 (1970).

²⁸³ W. Hawes and S. Trippett, *J. Chem. Soc., C*, 1465 (1969).

²⁸⁴ S. Trippett, "Organophosphorus Chemistry," Vol. 1, p. 13. Chem. Soc. London, 1970.

Waite and Tebby²⁸⁵ have recently reinvestigated the reaction of 1,2,5-triphenylphosphole (486) with DMAD and have shown that the product formed in this reaction has the structure 489, not the earlier assigned structure 490²⁸⁶ or other possible structures like 491, 492, and 493.²⁸⁵ The formation of 489 has been assumed to proceed through intermediates like 487 and 488 (Scheme 77).



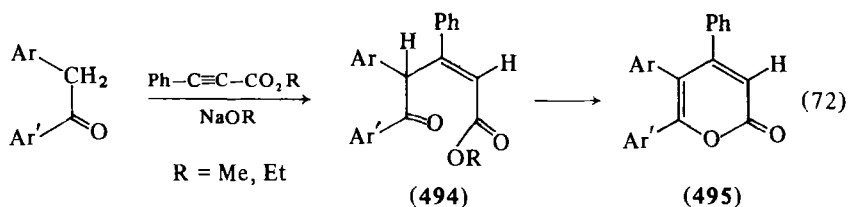
SCHEME 77

VI. Miscellaneous Nucleophiles

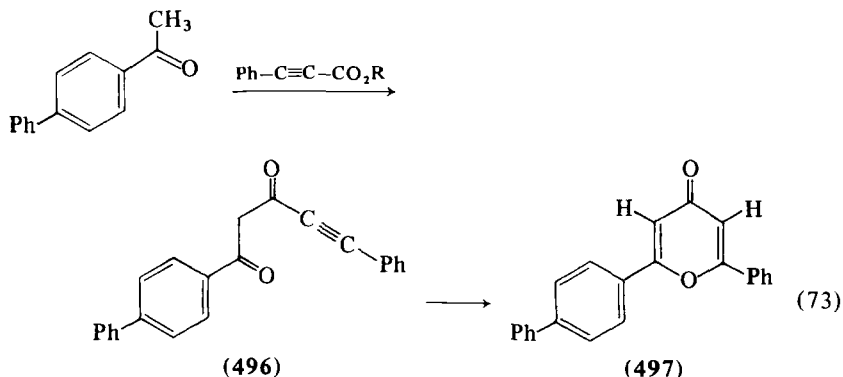
Carbanions derived from substances containing active methylene groups are known to react with acetylenic esters leading to heterocyclic compounds. Deoxybenzoins, for example, react with phenylpropiolates

²⁸⁵ N. E. Waite and J. C. Tebby, *J. Chem. Soc., C*, 386 (1970).

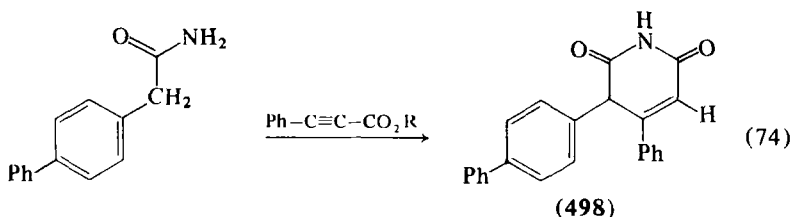
²⁸⁶ A. N. Hughes and S. Uaboonkul, *Tetrahedron* **24**, 3437 (1968).



in presence of sodium alkoxide to yield 2-pyrones (495) through the initially formed 1 : 1 adducts (494) [Eq. (72)].²⁸⁷ The reaction of 4-acetylbiphenyl with ethyl phenylpropiolate, on the other hand, gives rise to a condensation product (496), which can be further converted to a 4-pyrone (497) [Eq. (73)].²⁸⁸ Similar reactions have been observed with



other biphenyl derivatives, such as ethyl 4-biphenylacetate and 4-biphenylacetonitrile.²⁸⁸ The reaction of 4-biphenylacetamide with ethyl phenylpropiolate, however, gives a glutaconimide derivative (498) [Eq. (74)].²⁸⁸ The condensation of 2-pyridylacetate with ethyl phenylpropiolate has recently been reported to give a quinolizone derivative.²⁸⁹ The reaction of ethyl phenylacetates with ethyl



²⁸⁷ I. E. El-Kholy, F. K. Rafla, and M. M. Mishrikey, *J. Org. Chem.* **31**, 2167 (1966).

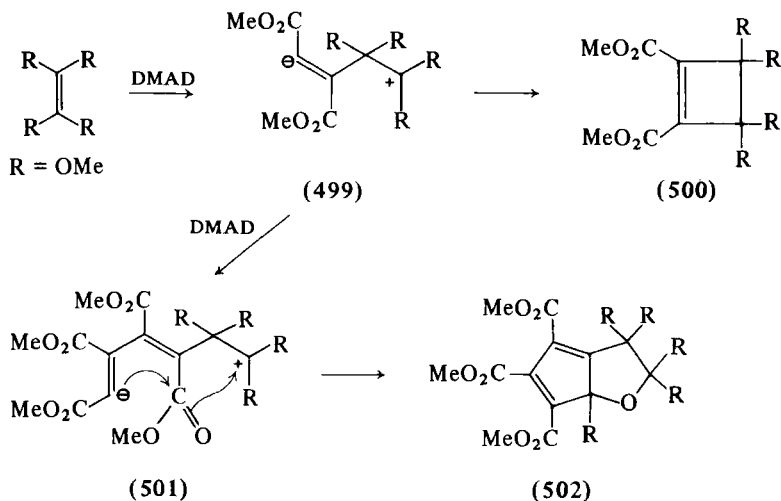
²⁸⁸ H. N. Al-Jallo, *J. Chem. Eng. Data* **17**, 513 (1972) [*CA* **77**, 151833 (1972)].

²⁸⁹ H. N. Al-Jallo and F. W. Al-Azawi, *J. Heterocycl. Chem.* **10**, 139 (1973).

phenylpropiolate, on the other hand, gives α -substituted β -(phenylethynyl) ketoesters.²⁹⁰

Acyloxyacrylates are conveniently prepared through the catalyzed addition of carboxylic acids to propiolic esters. Thus, the addition of acetic acid (iron salt) to methyl propiolate yields methyl 3-acetoxyacrylate.²⁹¹ Similar additions have been observed with benzoic acid to give the corresponding acrylic esters.

In the reaction of tetramethoxyethylene with DMAD, Hoffmann *et al.*²⁹² have recently reported the formation of a mixture of 1 : 1 and 1 : 2 adducts identified as **500** and **502**, respectively (Scheme 78).



SCHEME 78

Hendrickson and co-workers²⁹³ reported that triphenylarsine reacts with DMAD to give tetramethyl 1,1,1-triphenylarsole-2,3,4,5-tetracarboxylate (**503**). However, it was subsequently shown by the same workers²⁹⁵ that the product formed in this reaction is the adduct **505**, not **503** (Scheme 79). Recently, Ciganek²⁹⁴ has shown that triphenylarsine oxide reacts with DMAD to give the same adduct (**505**) (Scheme 80). He has further suggested that the formation of **505** in the reaction of triphenylarsine may proceed through a zwitterionic intermediate (**504**), which reacts with water to give triphenylarsine oxide

²⁹⁰ H. N. Al-Jallo and F. H. Al-Hajjar, *J. Chem. Soc., C*, 2056 (1970).

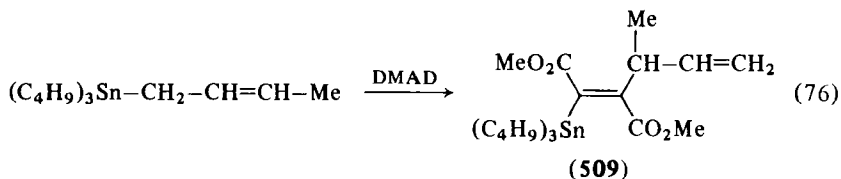
²⁹¹ L. A. Miller, U.S. Patent, 3,129,201 (1964) [CA 61, 9405 (1964)].

²⁹² R. W. Hoffmann, J. Gehlhaus, G. Steinbach, and H. J. Lindner, *Chem. Ber.* **106**, 1758 (1973).

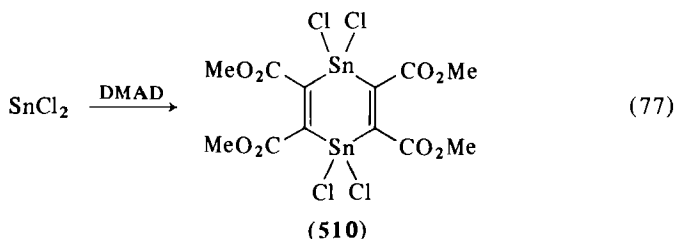
²⁹³ J. B. Hendrickson, R. E. Spenger, and J. J. Sims, *Tetrahedron Lett.*, 477 (1961).

²⁹⁴ E. Ciganek, *J. Org. Chem.* **35**, 1725 (1970).

Certain organostannanes have been shown to react with DMAD to give simple addition products. Thus, the reaction of allyltributylstannane with DMAD gives the 1:1 adduct **508** [Eq. (75)] whereas crotyltributylstannane gives the adduct **509**, occurring through an allylic type of rearrangement [Eq. (76)].²⁹⁶



Harrison²⁹⁷ has observed an interesting reaction of stannous chloride with DMAD to give a distannacyclohexadiene derivative (**510**), presumably formed through a stannacyclopropene intermediate [Eq. (77)].



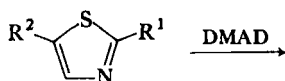
Note Added in Proof

Recent studies²⁹⁸ have shown that the product formed in the reaction of thiazole (**383a**) with DMAD is the adduct **512a** and not **384a**, as reported earlier.²³⁴ Similarly, the reaction of 2-methylthiazole (**383c**) with DMAD gives the corresponding adduct, **512c** (Scheme 81). The formation of the adducts **512a** and **512c** in these reactions have been rationalized in terms of the transformations of the initially formed addition products **384a** and **384c**, respectively, through the corresponding vinyl sulfide intermediates (**511**). An alternative pathway involves the [1,5]-sigmatropic rearrangement of the adducts **384a** and **384c** to give the products **512a** and **512c**, respectively (Scheme 81).²⁹⁸

²⁹⁶ C. Servens and M. Pereyre, *J. Organometal. Chem.* **26**, C-4 (1971).

²⁹⁷ P. G. Harrison, *Inorg. Nucl. Chem. Lett.* **8**, 555 (1972).

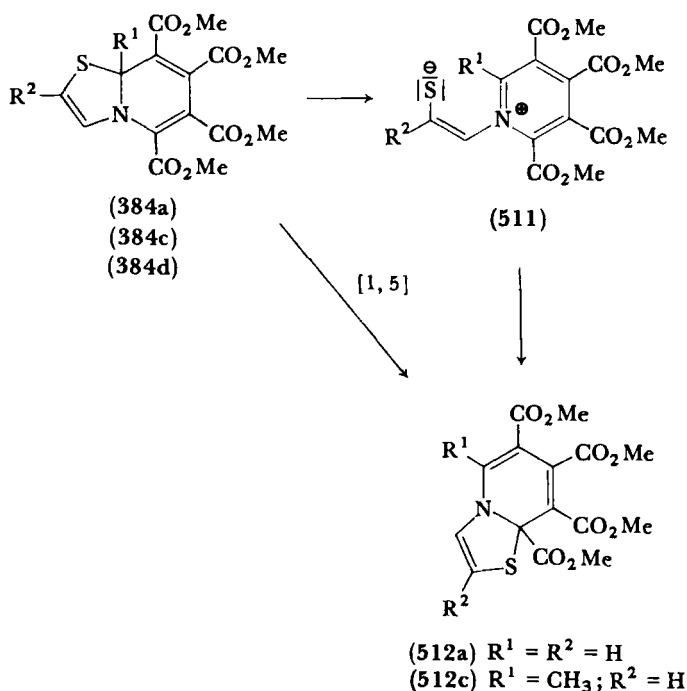
²⁹⁸ P. J. Abbott, R. M. Acheson, U. Eisner, D. J. Watkin, and J. R. Carruthers, *J. Chem. Soc. Chem. Commun.*, 155 (1975).



(383a) $R^1 = R^2 = H$

(383c) $R^1 = CH_3; R^2 = H$

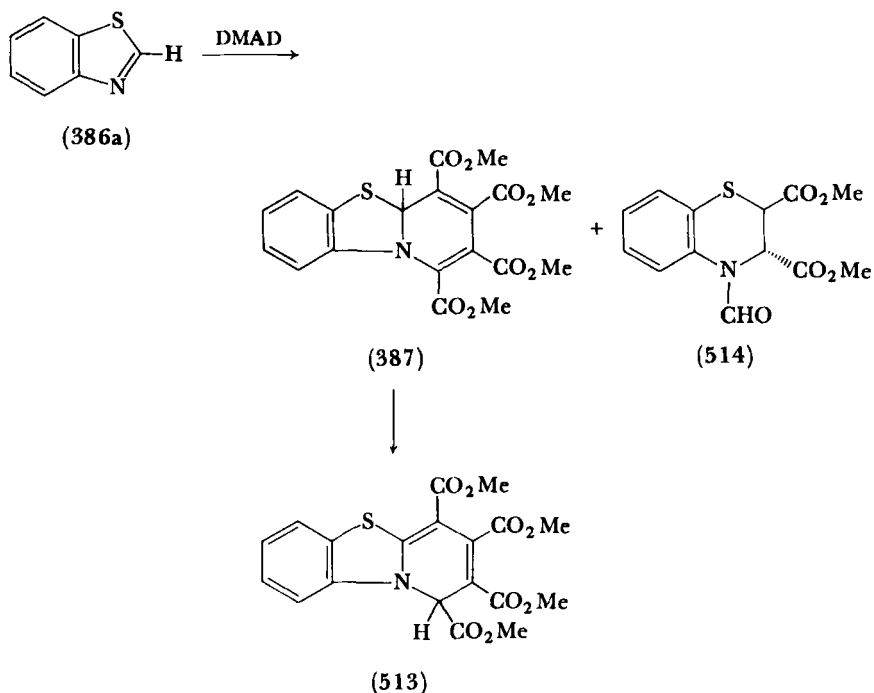
(383d) $R^1 = R^2 = CH_3$



SCHEME 81

The reaction of benzothiazole (**386a**) with DMAD has been shown to give a mixture of products consisting of **513** (34%) and **387** (small amounts).²⁹⁸ However, Ogura and co-workers²⁹⁹ have reported that benzothiazole reacts with DMAD to give a mixture of the initial addition product **387** and an abnormal addition product **514** (Scheme 82).

²⁹⁹ H. Ogura, H. Takayanagi, and K. Furuhashi, *J. Chem. Soc. Chem. Commun.*, 759 (1974).



SCHEME 82

ACKNOWLEDGMENTS

The authors thank Mr. B. Pandey and Mr. A. Mitra for their help in preparing this manuscript. Financial assistance from the Educational Development Center of I.I.T. Kanpur for the production of this manuscript is gratefully acknowledged.

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* A correction to this article appears in volume 19, p. xi.

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